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THE UNIVERSITY OF ALBERTA

EFFECT OF HYPOTHERMIA ON THE OXYGEN TRANSPORT AND OXYGEN CONSUMPTION IN THE ADULT RESPIRATORY DISTRESS SYNDROME

by

(C) OMKAR N. BHATT

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

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THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled Effect of Hypothermia on the Oxygen Transport and Oxygen Consumption in the Adult Respiratory Distress Syndrome

submitted by Omkar N. Bhatt

in partial fulfilment of the requirements for the degree of Master of Science in Experimental Medicine in the Department of Medicine

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Date April 16, 1976

Dedicated to my Wife

Suman

who bore with me lovingly and

patiently all through this project

at the cost of her own comforts

and ambitions.

ABSTRACT

The Adult Respiratory Distress Syndrome is a clinical descriptor applied to a state of progressive hypoxemic respiratory failure that occurs in association with several clinical disorders. This syndrome is seen in cases of shock, massive thoracic or non-thoracic trauma, fat embolism, burns, septicemia, acute pancreatitis, bacterial, viral and aspiration pneumoniae, drowning, and after open heart operations. There is progressively worsening hypoxemia despite administration of oxygen and use of currently available modes of therapy in Intensive Care Units.

Hypothermia is one of the therapeutic modalities that has been used in support of critically ill patients with the idea that it may reduce oxygen demands of the tissues and restore a balance between the available oxygen and its consumption. However, the exact role of hypothermia in hypoxemic respiratory states is far from clear. In fact, some reports have suggested that the hypothermia may prove more harmful than beneficial.

The present study was designed to provide an answer concerning the role of hypothermia in hypoxemic respiratory states by studying oxygen transport and consumption in an experimental animal model. Oleic acid 0.075 ml/kg. body wt. was injected selectively into the right heart circulation of mongrel dogs resulting in a reduction in pulmonary functions and acute hypoxemia which characterises the Adult Respiratory Distress Syndrome. Two groups of animals were

studied under controlled experimental conditions: Group I was maintained at normal body temperature whereas Group II was cooled to 34°C and maintained at this temperature level for twelve hours with subsequent rewarming to 37°C 'core' temperature.

Oleic acid injected into the pulmonary circulation induced severe arterial hypoxemia with an increase in ventilation perfusion imbalance, increase in dead space ventilation and a decreased lung compliance in both groups. Hemoglobin, hematocrit and pulmonary artery pressure were elevated whereas heart rate, systemic arterial pressure and cardiac output decreased. These parameters showed a similar trend during the entire observation period in both groups. However Group II dogs demonstrated a further fall in arterial oxygen tension, venous oxygen tension and an increase in venous admixture and shunt as compared to the Group I dogs.

It was observed that the induced hypothermia reduced both oxygen transport and oxygen consumption. However, oxygen transport was reduced to a greater extent than oxygen consumption. Animals in the hypothermic group were more hypoxemic and acidotic than control animals, especially on rewarming. The survival rates for the two groups were 33% and 82% for the Group II and Group I respectively at 22 hours in the 26 hour observation period.

From this study, it is concluded that hypothermia may, in fact, be harmful in acute hypoxemic respiratory failure.

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Omkar N. Bhatt

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TABLE OF ABBREVIATIONS

α	- Solubility coefficient for oxygen in solution
$A-aDO_2$	- Gradient between partial pressures of oxygen in the alveolar air and arterial blood.
ARDS	- Adult Respiratory Distress Syndrome
A.T.P.S.	- Ambient temperature, pressure and saturated with water vapour
B.T.P.S.	- Body temperature, ambient pressure and saturated with water vapour
CaO_2	- Content of oxygen in arterial blood (vols. per cent)
$C\bar{c}O_2$	- Content of oxygen in pulmonary capillary blood
$C\bar{v}O_2$	- Content of oxygen in mixed venous blood
Dynamic Lung Compliance	- Change in airway pressure over the range of fixed tidal volume (ml/cm H_2O).
$FECO_2$	- Carbon dioxide fraction in expired air
FEN_2	- Nitrogen fraction in expired gas
FEO_2	- Oxygen fraction in expired gas
$FICO_2$	- Carbon dioxide fraction in inspired gas
FIN_2	- Nitrogen fraction in inspired gas
FIO_2	- Oxygen fraction in inspired gas
Hb.	- Hemoglobin (gms/100cc.)
Hct.	- Hematrocrit
IRDS	- Infantile respiratory distress syndrome
$PaCO_2$	- Partial pressure of carbon dioxide in arterial blood (mm Hg)
PaO_2	- Partial pressure of oxygen in arterial blood
$PACO_2$	- Partial pressure of carbon dioxide in alveolar gas
PAO_2	- Partial pressure of oxygen in alveolar gas

$P\bar{c}O_2$ - Partial pressure of oxygen in pulmonary capillary blood ($P\bar{c}O_2 \cong PAO_2$)

$PECO_2$ - Partial pressure of carbon dioxide in expired gas

PEO_2 - Partial pressure of oxygen in expired gas

PIO_2 - Partial pressure of oxygen in inspired gas

$\dot{Q}s$ - Quantity of blood (liters/minute) flowing through pulmonary shunts and hence not oxygenated.

$\dot{Q}t$ - Total cardiac output (quantity of total flow in the lung)

R - Respiratory Quotient ($\dot{V}CO_2/\dot{V}O_2$)

SaO_2 - Percentage saturation of hemoglobin with oxygen

S.T.P.D. - Standard temperature (0°C); pressure (760 mmHg) and dry

$\dot{V}Co_2$ - Total carbon dioxide production

V_D - Physiological dead space (percent of tidal volume)

$\dot{V}_E$ - Total expired minute ventilation (ml/minute)

$\dot{V}O_2$ - Total oxygen consumption (ml/minute))

$$V_{BTPS} = V_{ATPS} \times \frac{273+t°C}{273+T°C} \times \frac{P_B - P_{H_2O \text{ at } T°C}}{P_B - 47}$$

$$V_{STPD} = V_{ATPS} \times \frac{273}{273+T°C} \times \frac{P_B - P_{H_2O \text{ at } T°C}}{760}$$

[T°C is the spirometer temperature

t°C is the body temperature]

V_T - Tidal volume

CHAPTER I

Introduction

A. Adult Respiratory Distress Syndrome

1) Definition

A syndrome of progressive hypoxemic respiratory failure (Wilson, 1970) occurring in a variety of direct or indirect pulmonary insults, has been recognised with increasing frequency in recent years. This syndrome, characterised by marked respiratory distress with restlessness, tachypnea, cyanosis, intercostal indrawing, radiologic evidence of diffuse pulmonary infiltrates, decreased effective pulmonary compliance and hypoxemia, has been labelled as the Adult Respiratory Distress Syndrome (ARDS) by Ashbaugh and Petty (1967, 1969). The name 'ARDS' was chosen because of the functional and structural similarities between this syndrome as it occurs in adults and the Infantile Respiratory Distress Syndrome (IRDS) or hyaline membrane disease.

The syndrome may appear anywhere between one to 96 hours (Lewin et al, 1971) after major body trauma and shock states. Often these patients fail to respond to the conventional modes of therapy and total body support available in Intensive Care Units so that mortality remains

high (Ashbaugh and Petty, 1972) and currently is about 50% from all causes.

The ARDS has been described under a variety of names which include: wet lung, septic lung, congestive atelectasis, post-traumatic pulmonary insufficiency, Da Nang lung, post-perfusion lung, pump lung, fat embolism, aspiration pneumonia, bacterial and viral pneumonia, drowning, respirator lung (Orell, 1971) progressive stiff lung, post-amniotic fluid embolism, oxygen toxicity, post-intracranial injury pulmonary insufficiency (Zimmerman, 1971), low flow lung syndrome or simply as 'shock lung'.

The consensus of opinion, however, is that Ashbaugh's term "ARDS" be used as this identifies a common clinical presentation (Garvey et al, 1975) in diverse conditions.

2) Etiopathogenesis

The 'shock lung' syndrome of progressive respiratory failure with worsening hypoxemia in spite of inhalation of increasing concentrations of oxygen implies severe disturbances of pulmonary function without implicating a single cause. The same pathologic end result follows a diffuse variety of insults: shock, sepsis, disseminated intravascular coagulation, fat emboli, aspiration, debris from massive transfusions, oxygen toxicity, central nervous system hypoxemia and adrenergic excess, overhydration and certain immunologic factors either alone or in combination

(Blaisdell, 1974). Since clinically so many factors are associated with the final picture, it is unlikely that there is any dominant single etiology.

The ARDS has been increasingly associated with shock. Shock, as we understand today, is a complex disorder and it is impossible to point to any particular facet of altered physiology of the body which leads to the Adult Respiratory Distress Syndrome. There is disagreement among experts as to whether the ARDS is a specific complication of the acute circulatory failure in shock or whether it is a pulmonary manifestation of generalised systemic injury (Lewin et al, 1971).

Pulmonary changes occurring in shock were first documented by Moon in 1936 who, from autopsy examinations, found congestion and atelectasis in the lungs of patients dying from shock. Burford and Burbank (1945) saw an increasing number of pulmonary injuries in combat casualties during World War II which led them to coin the word 'wet lung' to describe pulmonary complications of both thoracic and non-thoracic trauma.

Fegler and Bannister (1946) were the first to use the term "congestive atelectasis" to describe "the congestive and not hemorrhagic" condition of the lungs of animals kept for one hour at low (275-70 mmHg) i.e. below atmospheric pressure. Jenkins and his colleagues (1950) described the clinical syndrome of dyspnea, tachypnea, restlessness and cyanosis resulting from fluid overload which was often

resistant to oxygen therapy and had a high mortality rate. They carried out an interesting experiment in dogs in which a tourniquet was placed around an extremity to occlude limb circulation and a plexiglass window was inserted into the chest wall to observe the lung surface. Within a few minutes after release of the tourniquet, they observed minute spotty hemorrhagic areas on the lung surface. From this experiment they concluded that the lung lesions developed as a result of the blood coming from the damaged extremity and that left ventricular failure had nothing to do with development of these lesions as the left atrial pressure remained normal throughout the experiment. Rounthwaite, Scott and Gurd (1952) studied lung changes in experimentally induced hemorrhagic shock in dogs. Within two hours of inducing shock, they found gross congestion in the lungs, paticularly in the posterior basal parts, with "blue non-crepitant liver like areas". Kolff and his colleagues (1958) described pulmonary congestion and edema in patients during and after open heart operations while Halmagyi et al (1963) found similar changes in dogs following homologous blood transfusion and shock. Keller et al (1967) confirmed these changes following extracorporeal circulation. Sealy et al (1966) suggested that the lung, in fact, was a target organ in hemorrhagic shock since changes in the lung were as frequent as those in the heart and twice as frequent as those in the portal bed. They observed large confluent areas of hemorrhagic consolidation involving the lungs diffusely.

Schramel and his colleagues (1968) found that virtually every case of "congestive atelectasis" was preceded by a period of shock which had usually been treated adequately. They reported their x-ray findings of bilateral confluent densities, particularly in lower portions of the lung fields. These lesions were believed to be due to loss of pulmonary capillary integrity with pulmonary vascular congestion, edema and extravasation of blood and fluid into the lung. The role of increased pulmonary capillary permeability was also stressed by Teplitz (1968). According to him it was the extruded protein and not the water that was contributing to the pulmonary edema since the extruded protein not only represented the obstructive intra-alveolar foreign matter but "also serves as an osmotic force to allow for further transudation of fluid."

Pulmonary circulation, obviously, has a role to play in the genesis of the ARDS because the pulmonary capillary bed is the only vascular network that receives almost all of the cardiac output during each circulation. Long et al (1968) found an increase in pulmonary vascular resistance and an uneven distribution of ventilation and pulmonary perfusion. In addition, there was significant respiratory and metabolic acidosis which can lead to the increase in pulmonary vascular resistance (Kim et al, 1973) and could thus lead to the development of shock lung in the post shock period. That there was uneven distribution of ventilation and perfusion was confirmed by Germon et al (1968) who used I^{131} labelled

serum albumin macroaggregates to delineate the areas of decreased perfusion which, they suggested, were due to arteriolar vasoconstriction. However, Monaco et al (1972) found venous admixture to the extent of 35% in these patients which Powers et al (1972) felt was due to a drastic reduction in functional residual capacity.

The Vietnam war led to an increasing awareness of the problem of post-traumatic pulmonary insufficiency. Here was a situation wherein, with efficient air ambulance and field medical services, casualties were brought to the base hospitals within 15-60 minutes of the injury and resuscitated. However, many of these patients died later due to "a recurring syndrome with onset from the first to the third post injury day, of hypoxemic hyperventilation and symmetric patchy infiltrates on chest x-rays" (Ackroyd, 1968). Many of these were patients with non-thoracic trauma who were convalescing from other problems satisfactorily. Despite immediate resuscitation and all available supportive measures, including mechanical positive pressure ventilation, there was a progressive fall in arterial oxygen tension (PaO_2) and the course frequently was one of clinical deterioration and death due to pulmonary edema. These and other studies, from Da Nang Base Hospital in Vietnam, led to coinage of the term 'Da Nang lung' (Ackroyd, 1968). These patients often received massive blood transfusions; and fluid and electrolyte replacement with large amounts of crystalloids (i.e., Ringer's lactate solutions). Mills

(1968) suggested that the use of crystalloid therapy may have been a cause for pulmonary insufficiency, and Moore (1968) urged restraint in the administration of fluids following initial resuscitation since the excessive amounts of Ringer's lactate and sodium bicarbonate could aggravate any pulmonary insult that had already occurred with trauma. That fluid overload could do this was supported by Zimmerman (1971) who reported that ten out of 12 patients with post traumatic renal failure had acute respiratory failure and in eight of these ten patients this was related to fluid overload. All these patients improved rapidly with hemodialysis. This is in contradistinction to the view held by Moss et al (1972) who feel strongly that there is an "illogical overconcern for over transfusion", and in fact suggested that patients should have more prompt and complete restoration of the reduced blood volume. Bergofsky (1970) felt that there was no consistent evidence of lungs being primarily loaded with water, at least in the initial stages. According to him, the predominant changes were hyperemia, periarterial, capillary and interstitial edema and diffuse atelectasis. As a result the lungs, at post mortem examination, were heavy, congested and inflatable only with difficulty or not inflatable at all. These observations suggest that a major physiological counterpart of the anatomic observations would be a decrease in lung compliance as also evidenced by the need of having to use very high inflation pressures on a constant volume ventilator to

obtain adequate tidal volumes.

Hillen et al (1971) found a significant fall in the lung compliance in a hemorrhage-induced shock lung model in monkeys. It is not known whether the fall in lung compliance is a cause or effect relationship since loss of compliance could primarily be attributed to the loss of surface tension lowering agent (surfactant) as shown by Greenfield et al, (1968). Surfactant is a lipoprotein complex attached to an α-globulin and synthesized by the alveolar type II cells. Surfactant production depends upon an adequate pulmonary blood flow and alveolar integrity. Increased capillary permeability and microatelectasis theoretically could result from loss of surfactant itself since the heightened surface tension could cause transudation of protein-rich fluid from the capillary into the lung parenchyma (Bergofsky, 1970). Ashbaugh and Petty (1971) feel that the two may have a combined effect in decreasing lung compliance. There is damage primarily to the alveolar capillary membrane causing exudation of fluid into the alveolar spaces which interferes with the production and activity of surfactant (Clements, 1970) so that lungs become progressively stiff. In this connection the use of aerosolized dipalmitoyl lecithin, the major component of "surfactant", to stabilise alveoli and keep them from collapsing has proved disappointing (Chu et al, 1967), again suggesting that probably there is alveolar collapse due to exudation of fluid into the alveoli secondary to increased alveolar-capillary membrane

permeability.

Fluid exchange into the pulmonary interstitium and its absorption is another factor which is concerned with development of pulmonary edema. The influx and efflux of water, electrolytes and proteins from the intravascular compartment to the pulmonary interstitial space and the alveoli takes place across the capillary basement membrane. This transcapillary exchange obeys Starling's dictum (1896) of net pressure across the two surfaces of the capillaries. In this connection, left atrial pressure (pulmonary capillary wedge pressure) is the major intravascular force (hydrostatic pressure) promoting egress from the capillaries while colloid osmotic pressure exerted by the plasma proteins, mainly albumin, is the primary inward force. Normally the colloid osmotic pressure in the pulmonary capillaries is about 25 mmHg as compared to the capillary hydrostatic pressure which is about 10 mmHg (Robin, Cross and Zelis, 1973). The sequence of edema formation in the lung obeys balance of these pressures whether caused by fluid overload (high pressure edema due to increased capillary hydrostatic pressure) or decreased colloid pressure due to hemodilution or hypoalbuminemia (Stein et al, 1975). In this regard, reduced plasma colloid osmotic pressure (and hence reduced pulmonary colloid osmotic pressure) may have an important role to play. Morrissette et al (1975) showed that there was a direct correlation between low colloid osmotic pressure and fatal outcome of cardio-

respiratory failure. According to them, plasma colloid pressure less than 10 mmHg was incompatible with survival. Theoretically then, the use of albumin (James and Myers, 1972) should reduce the degree of edema formation. That this may be so is obvious from the observations of Skillman and co-workers (1970) who, in a clinical study, showed improvement in alveolar-arterial oxygen tension gradients in ten of 16 patients treated with albumin plus ethacrynic acid. However, Pontoppidan et al (1972) do not agree with this observation. They feel that with the increased capillary permeability, especially when secondary to sepsis (Vinocur, et al 1975), proteins like albumin also leak into the interstitium so that a colloid osmotic gradient cannot exist in a shock lung, and the leaked albumin, probably, would worsen the patients' condition (Teplitz, 1968). Stein et al, (1975) observed that measurement of colloid osmotic pressure - left ventricular filling pressure gradient was helpful in anticipating the risk of pulmonary edema in patients who were receiving large volumes of crystalloids and suggested that administration of colloids was appropriate to maintain plasma colloid osmotic pressure and thereby also decrease the risk of pulmonary edema. However, these authors were dealing with patients who were primarily hypovolemic and perhaps increased capillary permeability was not a problem at least in initial stages so that administration of colloid may be justified. The ARDS takes sometime to develop and at that stage there is an increased

capillary permeability so that albumin administered primarily for increasing extraction of fluid from the pulmonary interstitium, may not be serving any purpose except perhaps to contribute to the relative hypovolemia that these patients have on positive pressure ventilation.

Recently there has been some interesting data linking the ARDS with changes in the central nervous system which again emanated from the Vietnam war. About 85% of the soldiers who died of head injuries were found - at autopsy - to have a full blown picture of shock lung. These patients had lost little or no blood and were resuscitated with minimal or no fluid administration. Further, shock lung did not develop in those who had also suffered cervical cord transection. From these observations it appeared that (a) fluid administration could not be implicated as a causative agent; and (b) that brain damage could cause pulmonary edema only with an intact autonomic supply to the lung. Simmons (1968) raised intracranial pressure experimentally in baboons by the introduction of fibrin into the cisterna magna and this led to development of pulmonary edema. Sugg et al (1969) reported, from canine shock lung experiments, that when one lung was totally denervated (by removal) and then re-implanted prior to the induction of shock, it was protected from developing features of shock lung while in the same animal, the intact lung developed lesions in an unmodified form. These observations led Moss et al (1972) to propose a central neurogenic etiology for 'shock lung'. On

the basis of isolated cerebral hypoxemic arterial perfusion experiments, they postulated that the initiating trauma or shock state interfered with the hypothalamic cellular metabolism which in turn led to autonomically mediated increased pulmonary venular resistance and hence, increased capillary hydrostatic pressure and pulmonary edema. Moss (1974) in fact proposed a 'brain-lung' axis to also explain the toxic effects of high inspired oxygen concentration and increased oxygen tension (hyperbaric oxygenation) as primarily causing central nervous system damage, and pulmonary changes being secondary to the central nervous system damage.

Physiological Changes in the ARDS

The syndrome of Adult Respiratory Disress is becoming more common with the increasing number of extensive surgical resections; increasing use of cardiopulmonary bypass and rising incidence of major body trauma. The typical syndrome may be one of acute hypoxemia or it may be more insidious in onset with restlessness as the initial manifestation. Surprisingly, there is a paucity of clinical signs till very late despite severe physio-pathological alterations in the lungs. It is now well established that the lung is one of the target organs in shock and liable to damage following resuscitation. Physiological alterations consist in a drastic reduction of the Functional Residual Capacity (FRC) (Powers, 1972); decrease in pulmonary compliance (Sealy et

al, 1966; Ashbaugh and Petty, 1971) and increased dead space ventilation (Blaisdell, 1974). These changes are a result of the increase in the pulmonary arteriolar resistance; increased capillary permeability and decreased surfactant production and activity (Monaco et al, 1972). The salient laboratory findings are an increase in the respiratory minute ventilation with decreased $PaCO_2$, decreased PaO_2 on room air, increased $A\text{-}aDO_2$; leading eventually to hypoventilation with increasing $PaCO_2$; mixed alkalosis developing into metabolic acidosis and eventually respiratory acidosis (Dowd and Jenkins, 1972). Despite these changes, the spectrum of arterial hypoxemia may vary from mild form to catastrophic illness and whereas the former is spontaneously reversible and supportable with oxygen administration alone, the latter poses major therapeutic problems.

Pathological Changes in the ARDS

Pathological changes observed at autopsy of patients dying due to the ARDS, consist of the lungs being heavy, dark red or blue in color due to hemorrhagic edema and pneumonic consolidation (Orell, 1971). Diffuse hemorrhagic areas are particularly significant in view of the clinical observation of disseminated intravascular coagulation (DIC) which has been incriminated in the development of the ARDS (Patrick et al, 1970). Tissue injury, with or without hemorrhage, provokes a significant diminution of clotting

factors indicating that intravascular coagulation is occurring with secondary hemorrhages including hemorrhage into the pulmonary interstitium as an effect of the disseminated intravascular coagulation (Blaisdell, 1974). Airways are filled with hemorrhagic frothy secretions which are rich in albumin and higher molecular weight proteins like fibrinogen (Gump et al, 1971) as a result of the diffuse pulmonary edema.

Histologically there is marked interstitial edema (Hillen et al, 1971) with an increase in the number of type II pneumocytes. Generally, alveolar spaces are filled with fluid and white and red blood cell elements (Keller, 1967). There is microatelectasis due to thickening of the septa, capillary congestion, isolated areas of punctate hemorrhage and at times, confluent areas of frank infarction. Martin et al (1969) found edema, vascular congestion and alveolar hemorrhages in the lungs of soldiers dying in the immediate post-resuscitative period. Hyaline membrane formation and hyperplasia of the alveolar lining cells are seen, especially in lungs of burned patients and those receiving prolonged positive pressure ventilation with oxygen (Foley et al, 1968), which are located mainly in the alveolar ducts and respiratory bronchioles (Orell, 1971). These macroscopic and the microscopic alterations are encountered in all forms of critical hypoxemic illnesses described earlier.

3) Prognostic Factors

Ultimate outcome is dependent upon three major factors (Ashbaugh and Petty, 1972): (1) extent and severity of the original injury, (2) effectiveness of respiratory support, and (3) prevention of further injury by preventing fluid overload, sepsis and oxygen toxicity. Infection and oxygen toxicity need further description.

Infection

Infection superimposed upon the initial pulmonary damage represents a common and serious complication of the ARDS, and is currently the commonest cause of death (Ashbaugh and Petty, 1969, 1972; Lewin et al, 1971; Clowes et al, 1975). The infection, according to Ashbaugh and Petty (1971), is usually due to resistant gram negative organisms such as Pseudomonas aeroginosa and Klebsiella - Aerobacter species as well as Staphylococci and Serratia. This may, in itself precipitate respiratory distress and if the infection cannot be effectively controlled may prove fatal. In fact, Ashbaugh and Petty (1972) reported mortality of 69.4% in patients with pulmonary sepsis. Fulton and Jones (1974, quoted by Clowes et al, 1975) reviewed admissions to their hospital for trauma and found that hypovolemic shock accounted for only 7% of the patients with pulmonary insufficiency. "On the other hand, sepsis was present in 91% of those who had pulmonary failure requiring respiratory support and of all patients who became septic, 42% had

serious respiratory problems." Infections are of special importance in severely burned patients, those with widespread peritonitis and those with prolonged immunosuppression. Wilson et al (1969) reported mortality in the region of 95% in hypoxemic respiratory failure complicated with superadded sepsis. Hence it is of paramount importance to prevent infection and/or modify its course by treatment with antibiotics (Ashbaugh and Petty 1972) and to diminish the virulence and multiplication rate of the offending organisms without in any way compromising the host-defence systems. The latter has been shown to be achievable by using adjuncts like hypothermia (Cockett and Goodwin 1961; Williams and Cavanagh 1970).

Oxygen Toxicity

Oxygen breathed at high concentration and pressure has been shown to cause lung damage. Smith (1899) showed that if birds and small animals breathed oxygen at slightly less or slightly more than one atmospheric pressure, death resulted from acute respiratory failure within a few days. "The oxygen causes a general pneumonia which develops slowly to the stage in which the lungs are filled with fluid exudation....and the alveoli are found to be almost completely filled...and the blood vessels are extremely congested." Fisher et al, (1968) found that normal human volunteers exposed to hyperbaric oxygen at one or two atmospheres complained of substernal chest pain and pain on

coughing. There was a marked fall in vital capacity and pulmonary compliance after only 6-11 hours of exposure.

Oxygen whether breathed spontaneously or with mechanical ventilation can cause fatal pulmonary edema after 2-4 days exposure (Pontoppidan et al, 1972). Wolfe and his colleagues (1972) showed that breathing of high oxygen tensions decreased mucociliary activity while Suter et al (1974) showed that breathing of 100% oxygen led to absorption atelectasis and the $\dot{Q}s/\dot{Q}t$ were often increased within minutes of exposure to high inspired oxygen. Winter and Smith (1972) observed that high inspired oxygen concentration was associated with decreased surfactant production. Soloway et al, (1968) demonstrated that the major site of damage was the capillary endothelium and lesions produced as a result of oxygen toxicity were similar to the ARDS with formation of hyaline membranes, and interstitial and alveolar edema. Moss (1974) thought that the basis for oxygen toxicity was central rather than peripheral in that there was impairment of oxidative metabolism in the 'central neurogenic control center'. Centrally mediated effects of high concentrations of oxygen could also explain the frequent observation of blindness in the IRDS.

The role of pulmonary oxygen toxicity in patients with acute respiratory failure requiring high concenrations of oxygen is still uncertain. Most investigators have documented the development of pulmonary oxygen toxic

symptoms from high inspired oxygen tensions which are manifested by the rather sudden onset of severe hypoxemia which paradoxically is resistant to correction with further oxygen therapy (Patrick et al, 1970). Lipton and her colleagues (1973) issued a warning note against the use of hyperbaric oxygenation as 22 of their 30 patients treated with this modality died - according to them - due to oxygen toxicity superimposed upon the original pulmonary pathology. It has been argued that hypoxemia may offer protection against the pulmonary toxic effects of oxygen used in high concentrations (Hedley-White 1968). However, there is as yet no evidence to support this belief (Pontoppidan et al, 1972). In fact, current clinical evidence suggests that an FIO_2 of 0.5 or higher is likely to produce serious changes when used for more than two days. In treating the ARDS patients, it is often difficult to maintain adequate arterial blood gases without having to resort to the use of increasing concentrations of oxygen in the inspired air. In this situation a more suitable treatment may be to decrease the body's oxygen demands by lowering the metabolic rate, hoping thereby to enhance its tolerance to hypoxemia and thus avoid the consequences of oxygen toxicity.

4) Fat Embolism and the ARDS

Fat embolism is one of the factors known to lead to the Adult Respiratory Distress Syndrome (Ashbaugh and Petty,

1966; Fallat et al, 1974).

Presence of fat emboli in the pulmonary capillaries was recognized as early as 1862 by Zenker who observed fat droplets in the lungs of a railroad worker who had died shortly after crush injury to his chest and abdomen (quoted by Scuderi, 1941). Scuderi in 1941 described the classical pulmonary signs with fat embolism. He injected oleic acid intravenously in dogs and observed diffuse opacification of the lungs on x-rays, and at autopsy non-crepitance and hepatization of the involved lungs. Peltier (1956) confirmed the above findings and established that the pulmonary changes were a result of mechanical obstruction of the pulmonary vascular bed as well as chemical action of fatty acids. Sproule et al (1964) reported their clinical experience with the respiratory derangements in fat embolism and noted profound hypoxemia and widened alveolar-arterial oxygen gradients, while Ashbaugh and Petty (1966) felt that the respiratory failure was primarily responsible for the mortality associated with fat embolism.

It is well established that fatty emboli are liberated during conditions of trauma and shock (Peltier, 1968), and that these are flushed into the circulation due to fluid shifts in shock (Fuchsig 1967). The lungs bear the brunt of the damage caused by circulating emboli as these are arrested in the pulmonary capillaries resulting in an increase in alveolar dead space by widespread non-perfusion of the ventilated alveoli as a result of capillary blockage

(Blaisdell, 1974).

Fat droplets are freed as neutral fats from the cells, and fat depots such as bone marrow enter the circulation, are filtered in the lung capillaries where these are acted upon by lipase and hydrolysed to free fatty acids which initiate alveolar capillary damage, diminished lung surfactant and interestitial edema (Peltier, 1956, 1968). Such a configuration, i.e., varying degrees of hypoperfusion and varying degrees of elevated free fatty acids may in fact represent one of the basic patho-genetic mechanisms in Shock lung, post-perfusion lung as well as Adult Respiratory Distress Syndrome (Baker et al, 1969). Derks and Peters (1973) verified the similarity between pulmonary injury resulting from hypovolemic shock and that due to fat embolism and felt that the combination of shock and fat embolus was much more damaging to the lungs than shock alone.

That fat embolism does lead to the ARDS has been amply established both in clinical experiences (Ashbaugh and Petty, 1966) as well as in experimental studies by injecting oleic acid into the pulmonary circulation (Ashbaugh and Uzawa, 1968; Baker et al, 1969; Jones and King 1975). All these studies have shown a state of severe hypoxemic respiratory failure which invariably proved fatal unless supported with mechanical ventilation. Hence, the oleic acid induced experimental ARDS model can be used to study the changes in pulmonary structure and function as well as the

effects of various therapeutic modalities.

5) Therapeutic Implications in the ARDS

From the above discussion of the ARDS, it becomes clear that the patients have badly damaged lungs and altered cardiac functional status due to shock and sepsis, both resulting in severe hypoxemia and reduced oxygen delivery to the tissues. Treatment of these patients involves maintenance of adequate tissue oxygenation by means that will not aggravate pulmonary damage or further depress cardiac output (Fallat et al, 1974). It is imperative to avoid use of high inspired oxygen for prolonged periods of time as well as hyperbaric oxygenation for fear of pulmonary oxygen toxicity (Winter and Smith, 1972; Lipton et al, 1973). Positive end expiratory pressure improves arterial PO_2 by increasing functional residual capacity but it does so at the cost of decreasing cardiac output with consequent fall in oxygen delivery unless effective circulatory fluid volume is augmented (King et al, 1973). Besides, there is an increased incidence of pneumothoraces and pneumomediastinum which may further embarass cardiac function (Kumar et al, 1973). Recently extracorporeal membrane oxygenation has been advocated to improve oxygenation of blood (Converse Pierce II et al, 1973; Fallat et al, 1974) but this procedure is still experimental and restricted to a very few centers because of the cumbersome and expensive apparatus involved

as well as expert and highly trained staff needed to supervise its prolonged use. At the same time membrane oxygenation can lead to further blood damage by causing hemolysis and air embolism (Zapol, 1975).

The ARDS is, in addition, frequently complicated by sepsis, development of stress ulcers and massive gastro-intestinal hemorrhage, disseminated intravascular coagulation as well as altered mentation due to hypoxemia.

Obviously then the aims of therapy in the ARDS should be to

a) avoid any therapeutic modality that might further compromise the already compromised cardio-respiratory function; and

b) afford at least some degree of protection from the above mentioned complications. Hypothermia may be such a modality as it has been used more and more frequently in states of hypoxemia and critical ill health.

B. Hypothermia

1) Definition

Hypothermia in the homeotherm is defined as the lowering of body temperature below 35°C (Blair, 1964). Confusion exists over the precise meaning of the term as a

wide variety of definitions and their interpretations are used such as freezing, frozen sleep, hibernation, refrigeration and cryotherapy. The word 'hypothermia' was introduced by Talbot (1941) as a scientific entity to replace this range of descriptive terms. Despite this, clear distinction still needs to be made between hypothermia and hibernation as well as hypothermia induced for hyperpyrexia, which, in fact, is not hypothermia but an attempt to obtain normothermia since the temperature is brought down artificially to normal or slightly above normal range (Hitchcock et al, 1962). The word "Hibernation" cannot be applied to warm blooded animals since the state of true hibernation can only be induced in natural hibernators and not in homeotherms (Blair, 1964).

When a mammal hibernates its body temperature may fall to as low as 4°C (Bigelow et al, 1950). These animals seldom shiver and they may reduce their oxygen consumption to as low as 3-10% of normal. The observation that certain species of animals can and do survive drastically reduced body temperatures for longer periods of time (Gollan et al, 1955) stimulated a wide interest in attempting a similar state in non-hibernating warm blooded animals (Spurr et al, 1954). Hypothermia in fact, helped lay the foundations of open heart surgery by facilitating temporary circulatory arrest without causing any demonstrable tissue damage (Swan, 1973); simplified organ and tissue preservation for subsequent transplantation (Karow et al, 1974) and has been suggested

as a possible aid in the life support systems in man's quest for exploration of space (Cockett and Beehler, 1964).

2) Historical Perspectives

Hippocrates (460-377 BC) first suggested that the main purpose of breathing was to cool the heart. Plato (428-328 BC) held a similar opinion when he said: "As the heart might be raised to too high a temperature by hurtful irritation, the genie placed the lungs in its neighbourhood which adhere to it and fill the cavity of thorax in order that air vessels might moderate the great heat of that organ and reduce the vessels to an exact obediance" (quoted by Kao, 1974).

For a long time, physicians have recognised the benefits of cold therapy in reducing tissue damage, toxemia and debility resulting from excessively high body temperatures. Many early practices such as applying tepid sponges, ice packs and alcohol compresses are still popular. The Edwin Smith Papyrus ca. 3500 BC, (Breasted, 1930) recommended cold applications for wounds of the head and for infected or ulcerated breast. Cold water was used in treatment of sprains, fractures and gouty swellings, while ice was used to suppress hemorrhages and treat skin infections and head injuries. Virgil, in the "Bucolics" (Baynard, E. quoted in Swan, H., 1973) ascribed longevity with potency to men hardened by life long exposure to cold.

Cold water treatment was utilized by Antonius Musa, a freed slave, physician to Julius Caesar and later to Augustus (20 BC) to relieve the 'morning after' of his master, and in gratitude, Augustus is said to have decreed that the income of physicians be tax free (Floyer 1709, quoted in Swan, 1973). Cold water was used by Mercurialis Forli to relieve his renal colic pain little knowing that his patients did the same by running "to the spot in the nearby Arnus river where the cold springs entered" (Swan, 1973). Sanctorius, inventor of the clinical thermometer, described an apparatus for cold hydrotherapy which he called "the balneotorium" (quoted in Swan, 1973), recommended for fevers and other states of overactive metabolism. This is in no way different from the hypothermic suits used presently to cool patients.

Interest in the use of cold therapy and the benefits thereof was felt in the minds of notable physicians of later years as well. Historically, a Dr. Wright of the British Royal Navy in 1767 discovered this to his benefit as he lay on the deck of a ship prostrate with high fever, drenched by the rising cold sea waves which relieved him of his malaise and fever (Williams and Cavanagh, 1970).

First recorded therapeutic use of hypothermia was by James Currie (1797) who treated patients in the Liverpool infirmary. He completed first records of human temperatures in health, disease and under various experimental conditions as well as reported the lowering of body temperature of a healthy individual to 33.8°C, by immersing him in a brine

bath for 40 minutes. During the nineteenth century there were not many developments or reports in the literature of its use except for a brief note in the US Medical and Surgical Journal of 1836 urging cold baths over the hypogastric region in the treatment of nymphomania (Swan, 1973).

Major advances in the use of hypothermia came in the twentieth century and the most significant developments took place in the fifth and sixth decades. Smith and Fay (1940) used it to treat carcinomatosis hoping thereby to induce regression of the tumours. However, the most interesting observations were made by Dill and Forbes (1941) who reported upon the metabolic and respiratory changes met with in clinically induced hypothermia in schizophrenia. Hypothermia was used in a number of other clinical conditions such as leukemia, morphine addiction, intractable pain, Hodgkin's disease, subacute bacterial endocarditis, lymphogranuloma venereum, parasitic disease, undulant fever, chronic arthritis, tetanus, multiple sclerosis and encephalopathy (Talbot, 1941). Hypothermia remained an obscure therapeutic tool until the pioneering efforts of Bigelow and colleagues (1950) who first reported cooling dogs by surface immersion to a temperature of 25°C. They found a linear drop in oxygen consumption as the rectal temperature fell to 20°C. Bigelow and his colleagues were able to arrest circulation for varying lengths of time - five to twenty minutes - depending on the degree of

hypothermia and this was a stepping stone for open heart surgery. First successful clinical application of hypothermia was by Lewis and Tauffic (1953) for closure of an atrial septal defect. Hypothermia, thus, came to be widely used and this stimulated an interest in the study of physiological alterations during hypothermia in the living body. During the early fifties, another major development was the introduction of pump oxygenators for extra-corporeal circulation, which led to a temporary abandonment of hypothermia in some quarters as there was no doubt that the circulatory occlusion under simple hypothermia demanded precise preoperative diagnosis and allowed limited time for surgery. Besides, hypothermia was associated with complication of ventricular fibrillation noticed at temperatures below 29°C. However, subsequent research and development led to the eventual combination of extracorporeal circulation and hypothermia which facilitated requirements of the pump oxygenator system and helped in defining the exact role of hypothermia. Reeves and Lewis (1958) used hypothermia as an adjunct in critically ill febrile patients while Hitchcock et al (1962) used it to treat postoperative complications of gastrointestinal hemorrhage, severe brain damage and bone marrow depression secondary to overwhelming sepsis from generalised peritonitis. Hypothermia in the range of 32-34°C was used for periods varying from 4-20 days and it was noted that "concomitant with fall in temperature, the patient's

respirations improved, urinary output increased and the cardiac rate was slowed and stabilised" (Hitchcock et al, 1962). Gastrointestinal hemorrhage stopped in all of their patients. Harries and Lawes (1961) treated nine patients, all suffering from acute life threatening bulbospinal poliomyelitis, with moderate hypothermia (32-34°C) and reported a survival rate of 67%.

Recently, Matsukura and his colleagues (1970) reported eight survivors out of nine patients suffering from shock due to intestinal obstruction who were surgically treated under hypothermia (rectal temperature 30°C).

3) Physiological Alterations in Hypothermia

As the body temperature of warm-blooded animals falls, there is reduction in metabolic rate and therefore a diminished need for oxygen uptake. Bigelow et al (1950) found that whole body oxygen uptake was reduced by approximately 50% at 30°C and 65% at 25°C. Thus the heart, brain, liver and other vital organs can survive at lower temperatures for considerably increased periods of time when deprived of all or a portion of the blood supply (Blair, 1964). Mohri et al (1974) found a decrease in oxygen consumption to 76.9% at 35°C and 53.8% at 30°C of the precooling control level. Fisher et al (1957) concluded that hypothermia even to the extent of 23-24°C did not produce any morphologic alterations in various vital organs. It

would seem, at first glance, that the colder an animal gets the less oxygen would be required by a given organ. Theoretical extrapolation would suggest that there might be a temperature zone at which oxygen consumption ($\dot{V}O_2$) would be zero. However, it has been shown that there is considerable variation in oxygen requirements at lower temperatures for different organs. This is further affected by changes in the oxyhemoglobin dissociation curve, which along with changes in cardiac output and heart rate, affect oxygen available to the tissues. With the fall in temperature, the oxyhemoglobin curve shifts to the left so that less oxygen can be released, at the tissue level, from hemoglobin. At the same time oxygen requirements are also modified by the state of activity of the animal. With shivering, Dill and Forbes (1941) reported an increase in the oxygen consumption in the majority of their patients with induced hypothermia.

Studies of Bigelow et al (1950) have been the basis for all further studies. They found that there was a linear fall in the heart rate and respiratory rate. Cold narcosis supervened at 28°C and spontaneous respirations ceased a little later. However, even though the circulation was reduced, there was no abnormal fall in oxygen content during the passage of blood through tissues. In other words, the level of circulation was still adequate for the tissue demands. Rosenhain and Penrod (1951) concluded that in terms of physiological adequacy, both respiration and circulation

of the dog remained good until a short time before death. This was indicated by the constancy of venous oxygen content and arterio-venous oxygen difference though hematocrit rose from 42.3 at 38°C to 52.5 at 25°C temperature. Spurr and Horvath (1954) found that there was an exponential rather than linear relationship of the reduction of heart rate, and oxygen consumption; maximum fall in oxygen consumption resulted from mild to moderate levels of hypothermia.

All the above studies were done in animals cooled for relatively short periods of time (1 to 4 hours). Fisher and Fedor (1957) cooled their dogs to 29°C and maintained hypothermia for up to 26 hours. They found that the cardiac index fell to 76% in the first two hours of hypothermia and remained stable thereafter for the next 10-12 hours. Arterio-venous oxygen difference was directly proportional to the cardiac output, thus suggesting that the shift in oxyhemoglobin dissociation curve to the left at lower temperatures did not lead to tissue hypoxia. With the fall in cardiac output, arterio-venous oxygen difference increased, demonstrating that even after many hours of hypothermia, oxygen was still available and could be extracted by the tissues upon demand though the increased arterio-venous oxygen difference suggested that probably the oxygen delivery was insufficient to meet the needs of the tissues.

Severinghaus (1959) summarised the effects of hypothermia on the respiratory mechanism by saying that

"hypothermia alters virtually every measurable phenomenon in the field of respiratory gas transfer". The shift of the oxygen dissociation curve made less oxygen available to the tissues at a given tension in the blood. But with the small increase in dissolved oxygen in blood (Rosenhain and Penrod, 1951; Dittmer et al, 1958); and the reduced tissue demands for oxygen, the dissolved oxygen may supply a large portion of the metabolic needs. However, this could be complicated by a fall in cardiac output and thus decrease oxygen delivery. A further interesting facet was the discovery by Fleming (1954) that pH fell by 0.016 units/degree centigrade fall in temperature. The resultant acidosis could neutralize the left shift of the oxyhemoglobin dissociation curve.

Symbas et al (1971) observed a progressive decrease in the volume of external pancreatic secretion with a reduction of the body temperature. The flow of pancreatic juice stopped at 28°C. There was also a decrease in serum lipase and amylase concentrations. They suggested that this might be of value in treatment of acute pancreatitis. Blair et al (1962) found that though there was a fall in heart rate due to depression of the sino-atrial node and the bundle of His, this improved cardiac filling and stroke volume.

Besides its salutary effects on oxygen balance, hypothermia has been shown to be safe because it does not affect 'milieu intereur' to any significant degree. There are no significant changes in the serum electrolytes and carbon dioxide combining power (Fleming, 1954; Deterling et

al, 1955; Reeves et al, 1958) even when the temperatures are lowered to 25°C (Somasundaram et al, 1970).

4) Hypothermia in Acute Hypoxic States

Cerebral Hypoxia

Neurological damage, temporary or permanent, follows cerebral hypoxia. This may be immediate or delayed. Williams and Spencer (1958) reported on the use of total body hypothermia to treat cerebral anoxia following cardiac arrest. Their success with four patients led to further trials and animal experimentation both of which demonstrated its beneficial effects (Rosomoff et al, 1960). Harley (1964) summed up the rationale of using hypothermia by observing that it a) minimised damage to the neuroglial tissue and thus reduced any associated cerebral edema or swelling, b) improved the balance between cerebral oxygen availability and its demand by the brain and (c) it prevented hyperpyrexia which could result from hypoxic damage to the thermoregulatory mechanism.

Hypothermia has been found useful in reducing cerebral swelling and lowering the intracranial pressure following head injury and neurological operations. Shapiro et al (1974) reported therapeutically significant reduction of raised intracranial pressure by the use of barbiturate augumented hypothermia.

Asphyxia Neonatorum

Asphyxia neonatorum is a congenital condition in which the lungs are lined with a clear hyaline membrane through which oxygen finds it difficult to diffuse into pulmonary capillaries. The mortality rate is as high as 40-60% due to progressive hypoxemia. Babies who survive, may be left with irreparable brain damage. Treatment with 100% oxygen is only rarely successful and in addition carries the risk of further pulmonary damage and blindness due to retrolental fibroplasia. The concept of cooling newborn babies is not new. It has been practiced for centuries all over the world. "Sarah Parks gave stillbirth to a baby boy.... A young doctor, assisting the Parks' regular physician begged an opportunity to experiment with an idea he had to rouse the lifeless infant. A tub of ice was ordered and the young doctor plunged the baby into it. Out came the screaming fifteenth little Parks and he was named Gordon, after the doctor who prodded him to life." (Quoted from Miller 1971).

Dunn and his colleagues (1969) treated 28 neonates with hypothermia following their standard resuscitation. During hypothermia there was a mean increase of 6.4 apgar units and all infants began to breathe with 89% survival. None of these had any neurological abnormalities. This is in contrast to the earlier study reported by Drage et al (1964) who had survival figures of only 44.7%. Miller (1971), a strong advocate of hypothermia in neonatal resuscitation, demonstrated beneficial effects of hypothermia in treating

neonatal asphyxia as being due to (a) reduced oxygen demands of the neonate, and (b) probably better utilization of available oxygen carried in solution at lower body temperatures. By maintaining the baby in a well oxygenated condition for several hours, acid base balance was restored to normal limits, the hyaline membranes became enzymatically dissolved and on rewarming, the baby could breathe normally. Miller assisted by his pediatrician wife Faith (who died in 1971) presented their data at a number of meetings, but the method has not been accepted widely because the "minds of most doctors have remained closed to the vast body of knowledge which would make it possible for them to utilize hypothermia..." as a life-saving therapeutic modality (Henry Swan, 1973).

Shock States

The fundamental defect in shock is an inadequate supply of oxygen to meet the tissue requirements (Thal, 1971). As a result of the cellular hypoxia, cell metabolism suffers and a vicious circle is set up which leads to further worsening of the shock state and this may prove fatal. Hypothermia has been used in shock to reduce body oxygen demands so that the available oxygen is better utilized and distributed for the conservation of vital organ function (Blair, 1962). This concept has been especially useful in the management of tissue hypoxia and peripheral vascular collapse in septic shock (Allen et al, 1960; Cockett and Goodwin, 1961).

Reeves and Lewis (1958) carried out cooling to 35-36°C in critically ill febrile patients "in whom all possible modes of treatment were exhausted and in whom fatal outcome was thought likely", and found significant gains in that there were three survivors in the cooled group and none in the control group.

Friedman et al (1956) felt that the successful use of hypothermia in infection was due to its protection of the host anti-bacterial defence system and showed that the animals in hemorrhagic shock coped with a dose of bacteria injected during hypothermia period that would have been fatal to the normothermic dogs. This was confirmed by Fedor et al (1958) who observed that the initial leukopenia which is characteristically described in hypothermia, was not only transitory in nature but was followed by an increase in band neutrophils. These leucocytes retained the capacity of phagocytosis both during the phase of cooling and upon rewarming. Allen et al (1960) used hypothermia to treat four patients, all critically ill with septic shock (one of the patients being a female physician), after they had failed to respond to the accepted therapeutic regimens. Three of these survived and the fourth also responded to hypothermia but succumbed later to massive hemolysis from an incompatible blood transfusion. (Allen et al, 1960) felt that the beneficial effects of hypothermia were due to the retardation of bacterial growth and metabolism. Cockett and Goodwin (1961) found hypothermia a useful therapeutic agent

in the management of bacteremic shock following urological operations.

Clein and Couves (1962) agreed that hypothermia protected dogs subjected to hemorrhagic, traumatic or endotoxic shock but noted that hypothermia did not influence the outcome once shock was established. Blair et al (1962) were convinced that the 'coup de grace' in endotoxic shock or shock due to some other causes, was anoxia due to a disparity between the oxygen demands of the cell (MRO_2) and oxygen delivery to it (CDO_2) by the circulation. Death supervened when MRO_2:CDO_2 disparity passed a minimal critical ratio. MRO_2 is 30% of the normal at 30°C and hence the balance may be restored, if only partially, at lower temperatures. Thal (1971) concluded that the use of hypothermia as an adjunct to other modes of shock therapy was logical. Williams and Cavanagh (1970) utilizing this logic found, in an experimental canine study, that blood pressure was maintained at more normal levels in dogs receiving endotoxin and hypothermia (30°C) than those receiving endotoxin alone.

An interesting example of the protective effects of hypothermia is the miraculous survival of an 18 year old stowaway, Amando, who journeyed from Havana to Madrid hidden in the confined space of the landing gear of a DC-8. The plane was flying at an altitude of 29,000 feet and took nine hours to reach Madrid. On reaching Spain, when the engines were turned off, the boy fell to the ground unconscious but

was alive and well. This was clearly a case of extreme hypoxia (PIO_2 is 38.4 mmHg at 29,000 feet) and his survival was due to the hypothermia induced at that altitude (air temperature is -4°C at 29,000 feet) which increased his tolerance to hypoxia (Pajares and Merayo, 1970).

5) Hypothermia - Possible Role in the ARDS

Hypothermia has become useful in the care of surgical patients, as an adjunct in cardiac and neurosurgical operations and in tissue and organ transplantation because of its potential advantage of reducing metablic activity. This is its basis for use in critically ill patients where an imbalance exists between the tissue demands of oxygen and the available oxygen delivery (Blair 1964). Hypothermia may have a place in the management of critically ill patients with the ARDS where the oxygen extracted from the air by damaged lungs is insufficient for the tissues. By reducing metabolic activity, it reduces oxygen demands and hence may restore the balance at least partially so as to (a) prevent further tissue hypoxia and (b) reduce demands on the lungs for more oxygen and allow valuable time during which lungs would, hopefully, heal from the initial insult as well as the insult from high ventilator pressures and high oxygen concentrations (Blair, 1964).

Hypothermia has been used in clinical practice for the past 25 years and has been found safe, easily available, and inexpensive. It has been used for short as well as for

prolonged periods (Hitchcock et al, 1962; Harries and Lawes, 1967) without any complications. Although warm blooded animals can be cooled from 36°C to 0°C, the lower the temperature, the greater is the risk from physiological alterations. The specific effects of lowered body temperature upon organs such as heart limit the level to below which the body can be safely cooled in the critically ill patient. A temperature range of 32°-34°C has been found to provide a linear drop of 50% in oxygen consumption without any other noticeable side effects (Williams et al, 1958; Blair, 1962; Harries and Lawes, 1961).

Besides its effect of reducing oxygen demands, hypothermia has been shown to be a beneficial adjunct in the management of gastrointestinal complications, sepsis, toxemia of acute pancreatitis (Symbas et al, 1971) and cerebral injury (Harley, 1964). These complications, either individually or in combination, are associated with the ARDS, hence the added justification for the use of hypothermia in the ARDS.

C. Plan of Study

Hypothermia has been recommended in the treatment of the ARDS (Wilson et al, 1969; Converse Pierce II et al, 1973; Zapol, 1975) though there are others who have expressed the feeling that hypothermia may not prove useful

(Bryan Brown, 1973). There is as yet no study to support or contradict these beliefs.

1) The Hypothesis

If hypothermia has to have a therapeutic role in the Adult Respiratory Distress Syndrome, it should improve the balance between oxygen supply and its demand by the tissues. An ideal situation in hypoxemic ARDS would be to aim at decreasing the oxygen consumption without decreasing the supply and transport of oxygen to the tissues.

The studies of Mohri et al (1974) and Kent and Converse Pierce II (1974), conducted in normal healthy uniformly cooled dogs, show (Fig. 1) a fall in oxygen consumption as well as oxygen delivery as the body temperature is lowered from 37°C to 30°C. However with the results of Mohri et al the drop in oxygen consumption was greater than the oxygen delivery while with the Kent and Converse Pierce II (1974) study, the reverse happened. In view of these conflicting results, it is not possible to predict the trend in hypoxemic critically ill patients. The purpose of the study reported here was to determine if hypothermia produced a greater decrease in oxygen consumption than that in oxygen delivery to the tissues in hypoxemic respiratory failure.

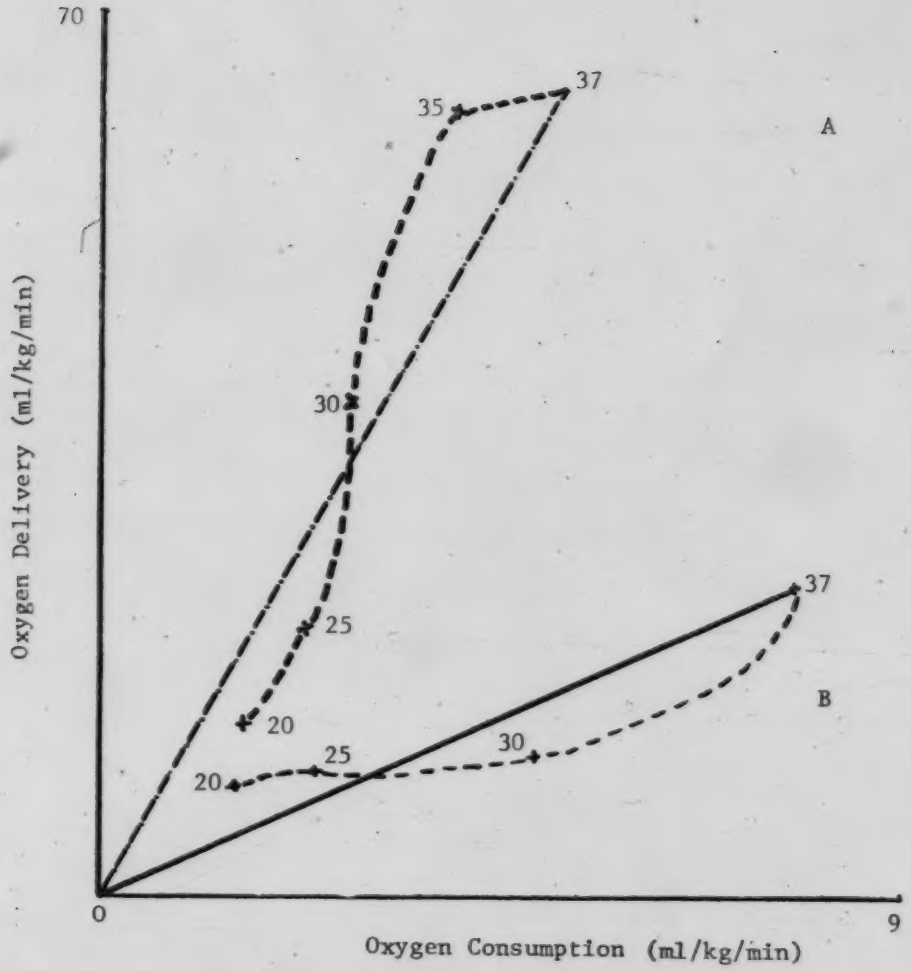

Figure 1 Oxygen delivery versus oxygen consumption from 37^{o} - 20^{o}C. From the data of Mohri et al 1974 (A) and Kent and Converse Pierce II 1974 (B)

2) The ARDS Model

In order to simulate the clinical situation of severe hypoxemia and critical illness, the oleic acid induced ARDS lung model (Ashbaugh and Uzawa, 1968; King et al, 1971; Jones and King, 1975) was used. In this model it is documented that there is a 35-50% drop in PaO_2; increase in $A\text{-}aDO_2$; increase in shunt and dead space ventilation as well as fall in lung compliance and functional residual capacity.

3) Range of Induced Hypothermia

Hypothermia was induced in the range of 33-34°C because:

a) This is the range where a linear drop in oxygen consumption has been shown consistently in all studies.

b) This temperature range has been shown to be safe for use for short term or prolonged periods (Reeves and Lewis, 1956; Hitchcock et al, 1962; Harries and Lawes, 1961). A temperature range of 32-34°C is safe, easily obtainable and is not accompanied by the complications of 'after drop' and myocardial arrhythmicity (Blair, 1969).

c) There are no documented changes in the water and electrolyte balance in the body.

CHAPTER II

Materials and Methods

A. Materials

Twelve adult healthy mongrel dogs were used for this study. These were randomly divided into two groups, "Control" (Group I) and "Hypothermia" (Group II).

The dogs were allowed only fluids to drink for twenty-four hours preceding the experiment. On the day of the experiment, the fasting animal was anesthetised with a slow intravenous injection of pentobarbital sodium (30 mg/kg body weight). Anesthesia was maintained for the duration of the experiment with continuous intravenous infusion of thiopental 0.2 mg/kg body weight/min. In addition, succinylcholine (0.5 mg/min) was injected as a continuous infusion to avoid spontaneous respiratory effort, muscle movement and shivering. The animals were placed in a supine position on the operating table and intubated using a cuffed endotracheal tube. Intermittent positive pressure ventilation with room air was instituted with an animal respirator (Harvard 607-Constant volume) at a fixed rate of 20 breaths/min. The tidal volumes were adjusted in each animal to provide $PaCO_2$ of 20-25 mmHg which usually resulted from a tidal volume of 15-20 ml/kg body weight. This was

kept constant for the duration of the experiment.

Polyethylene catheters were placed in the abdominal aorta and the inferior vena cava via a cutdown over femoral vessels in the groin. The aortic catheter was used for continuous monitoring of arterial pressure, for obtaining arterial samples for blood gas analysis, and for withdrawing blood for the measurement of cardiac output. The vena caval catheter was used to infuse dextrose 3.3% in 0.3% sodium chloride at a rate of 5 ml/kg/hr. A Swan-Ganz balloon-tipped flow directed catheter (#5F) was placed in the external jugular vein, threaded into the right ventricle and on into the pulmonary artery by observing pressure wave tracings on an oscillographic recorder (Electronics for Medicine IRC4). Blood pressures were obtained using Statham (P-23DB) transducers. In addition to providing pulmonary arterial blood pressure, the Swan-Ganz catheter was used for taking mixed venous blood samples for gas analysis and injecting dye for cardiac output measurement. Airway pressure was recorded using a Statham (PM5) differential transducer and a chart recorder (Gilson Medical Electronics, Middleton, Wisc.). A temperature probe (Yellow Springs) was placed in the mid-esophagus and a mercury thermometer placed 5-10 cm inside the rectum recorded the body temperature. Heart rate was read from Lead II E.C.G., displayed and recorded, along with systemic and pulmonary artery pressures, via the chart (Electronics for Medicine) recorder (Fig. 2). Tidal volume and expired minute ventilation were measured at ambient

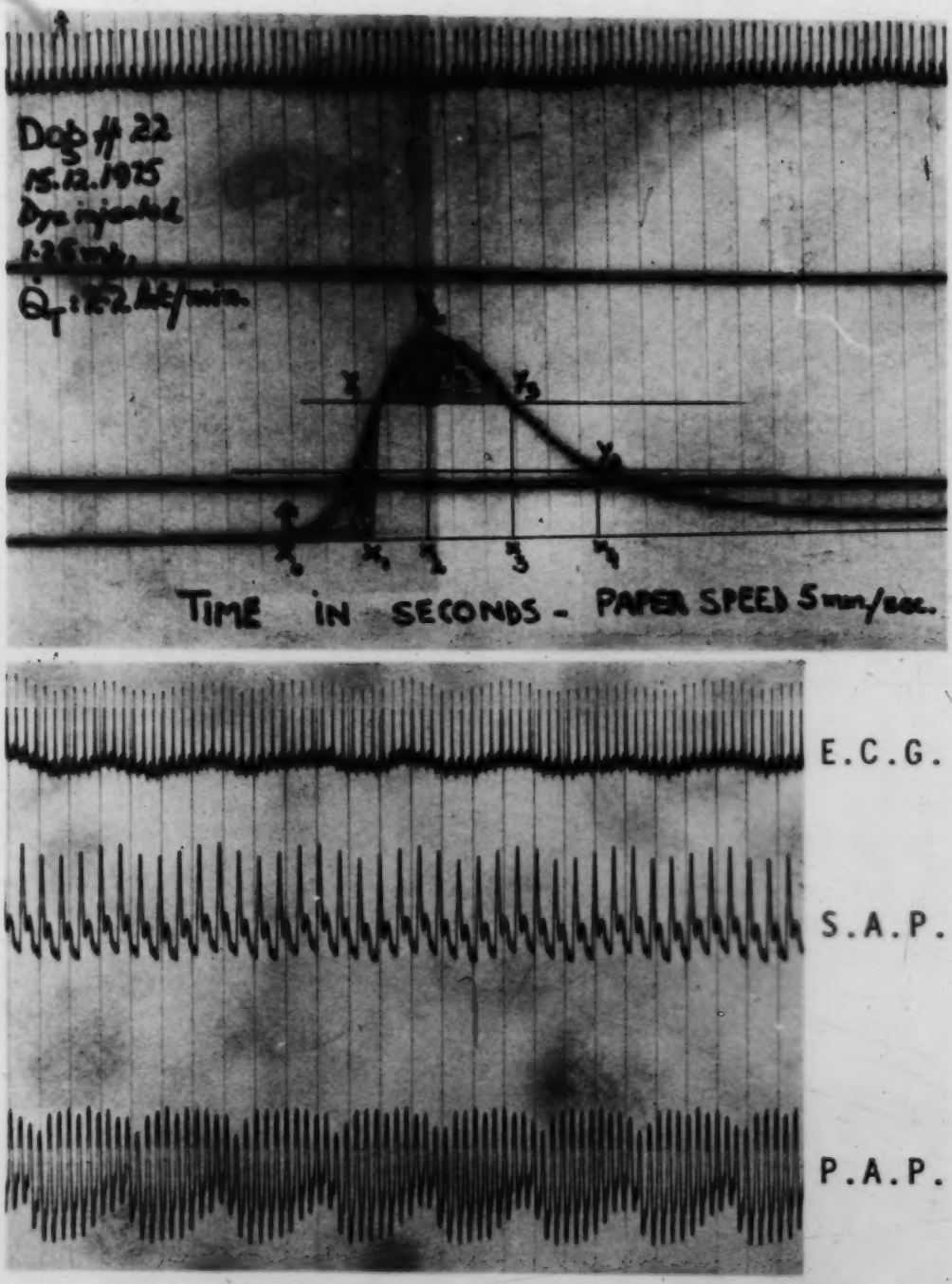

Figure 2 Photograph of an actual dye dilution curve (top), and a tracing of E.C.G., system and pulmonary artery pressures (bottom).

temperature and pressure by collecting 10-15 breaths from the expiratory port of the ventilator into a Standard recording Vitalometer (Collins).

In addition to the above, the following parameters were also measured:

Hemoglobin:

Hemoglobin concentration was measured using the standard ferricyanide technique (Davidsohn and Henry, 1969). Venous blood, 0.02 ml, was added to a 5 ml aliquot of Drabkin's solution (sodium bicarbonate 1.0 g; potassium cyanide 0.05 g and potassium ferricyanide 0.20 g in 1000 ml distilled water). This was allowed to stand for 15 minutes. Ferricyanide converts the hemoglobin iron from the ferrous to the ferric state to form methemoglogin which combines with potassium cyanide to produce stable cyanmethemoglobin. Density of the color produced was then read from a colorimeter (Klett-Summerson Photoelectric - colorimeter Model 800-3). The reading thus obtained was multiplied by the appropriate calibration factor for the Drabkin's diluent solution determined earlier using a hemoglobin standard. Hemoglobin concentration was obtained in grams per 100 ml blood.

Hematocrit:

Venous blood was drawn into a heparinised micropipette by capillary action. This was centrifuged in a special

hematocrit centrifuge (Readacrit) for 5 minutes to obtain hematocrit reading.

Cardiac Output:

Cardiac output was measured by a dye-dilution technique using Indocyanine Green. Dye, 1.25 mg, was injected into the pulmonary artery catheter and arterial blood was withdrawn into a 50 cc heparinised glass syringe attached to a constant infusion-withdrawal pump (Harvard Model 940). A Waters XC-302 cuvette was interposed in the system so that the concentration of dye in the blood flowing through it could be read from a densitometer (Waters X-301). The densitometer output was recorded on the chart recorder. In a typical measurement the chart paper speed was 5 mm/sec. and the area under the dye dilution curve was calculated by the method of Williams et al (1966). In this analytic technique, (Fig. 2), the section of the indicator dilution curve before the falling exponential segment is assumed to be a sequence of three parabolas: A_1, A_2 and A_3; the remaining curve is analysed as a single exponential. Geometric construction involved in the analysis requires the selection of a peak point Y_2. A horizontal line through upper third of the peak height (Y_2-X_2), perpendicular to it, gives points Y_3 and Y_1. Perpendicular lines dropped from Y_3 and Y_1 provide points X_3 and X_1. Another point Y_4 is obtained by bisecting the line Y_3 -X_3 and the perpendicular dropped from Y_4 provides X_4. The area under the curve is calculated from the standard

formulae for the areas under parabolas and exponentials:

$$^2/_3\ Y_2\ (X_3 - X_1) + Y_1\left[\frac{X_3}{3} + \frac{10}{7}\ (X_4 - X_3)\right]$$

where X_0 is the beginning of the curve and

Y_1 is the height of line $Y_1 - X_1$;

Y_2 is the height of line $Y_2 - X_2$;

X_1 is the distance $X_0 - X_1$;

X_3 is the distance $X_0 - X_3$;

X_4 is the distance $X_0 - X_4$.

All measurements are made in millimeters and the resultant area is in mm^2. From this, with the known dye concentration and the time in seconds, cardiac output was calculated, using a programmable desk calculator.

Blood and Expired Gas Analysis and pH Estimation:

Blood and expired gases were measured using an Instrumentation Laboratories 113 system equipped with a variable temperature water bath and electrodes for measuring PO_2, PCO_2, and pH. The PO_2 electrode measures PO_2 amperometrically by producing a current at a constant polarizing voltage which is directly proportional to the tension of oxygen diffusing to the reactive surfaces of this electrode. The electrode is covered by a plastic membrane permeable only to gases and not to contaminants and the reducible ions of the blood sample.

Measurement of pH is done with a pH electrode that works on the principle of establishing a potential, across a

thin glass membrane, whose magnitude is proportional to the difference in pH of the two solutions separated by this membrane. Contained on one side of this membrane is a solution of constant pH while in contact with the other side is the solution of unknown pH. Between these two surfaces a potential difference is established which is related to the pH of the unknown solution.

PCO_2 measurement is an adaptation of pH measurement. PCO_2 is measured potentiometrically by a combination of pH glass and a reference electrode arranged behind a gas permeable membrane. When exposed to carbon dioxide, CO_2 diffuses through this membrane in proportion to the PCO_2 difference across the membrane. Carbonic acid is formed and changes in carbonic acid are sensed as a change in pH of the electrolyte.

Arterial and mixed venous blood samples were obtained anerobically in heparinised glass syringes. The blood gas electrodes were calibrated with gases of known PO_2 and PCO_2 and the pH electrode was calibrated using commercial pH standards. Temperature of the water bath was adjusted to the dog's body temperature at the time of taking samples. Saturation of oxygen was obtained from the equation of Rossing and Cain (1966) which utilizes values: pH, PaO_2 and body temperature to calculate oxygen saturation.

Expired gases were also measured using the blood gas system. Expired air was collected over 5-10 minutes in an air tight balloon, and a 20 ml sample of this gas was

introduced into the gas analysis system to obtain the partial pressures of oxygen (PEO_2) and carbon dioxide ($PECO_2$).

The animals were ventilated with 100% oxygen for 20 minutes and both arterial and mixed venous blood samples were again analysed for PO_2, PCO_2 and pH to determine true shunt. Degree of true shunt was compared to the degree of venous admixture (true shunt + decreased ventilation - perfusion ratio). Both true shunt and venous admixture were calculated using the shunt equation shown in Section E (Calculations). True shunt is determined during 100% O_2 breathing while venous admixture was determined during room air breathing.

All the above parameters were measured as baseline data (before oleic acid injection) as soon as the tidal volume and PCO_2 were stabilised with the animal fully controlled on the respirator.

B. Fat Embolism - Injection of Oleic Acid

Following collection of baseline data, the Swan-Ganz catheter was withdrawn into the right ventricle. Oleic acid 0.075 ml/kg body weight was injected slowly through this catheter and the catheter flushed with 5 cc. normal saline to ensure a thorough mixing so as to obtain a uniform fat embolisation in the pulmonary circulation. The catheter was then re-advanced into the pulmonary artery where it remained

for the duration of the experiment.

C. Time Sequence of Readings

Dogs were divided into two groups. Group I (control) was observed for the entire experiment at normal body temperature (Fig. 3). Measurements were repeated two hours after the injection of oleic and at four hourly intervals for the subsequent 24 hours. In the hypothermia group (Group II), after the completion of the two hour post-oleic acid readings, the dogs were cooled to 33.5-34°C by covering them in rubberised blankets through which an ethanol solution circulated at a temperature of 5°C from a hypothermia unit (Aquamatic K thermia unit, Gorman-Rupp Industries Div., Bellville, Ohio). The dogs were maintained at 33.5-34°C for 12 hours during which three sets of readings were taken at four hour intervals. At the completion of this period of hypothermia, the animals were warmed to 37°C by circulating a warm solution through the blankets. Three more readings were taken at four hour intervals.

D. Pathological Examination

Pathological examination consisted of postmortem examination and histological study.

Postmortem examination was carried out in all dogs at the termination of the experiment. The chest was opened

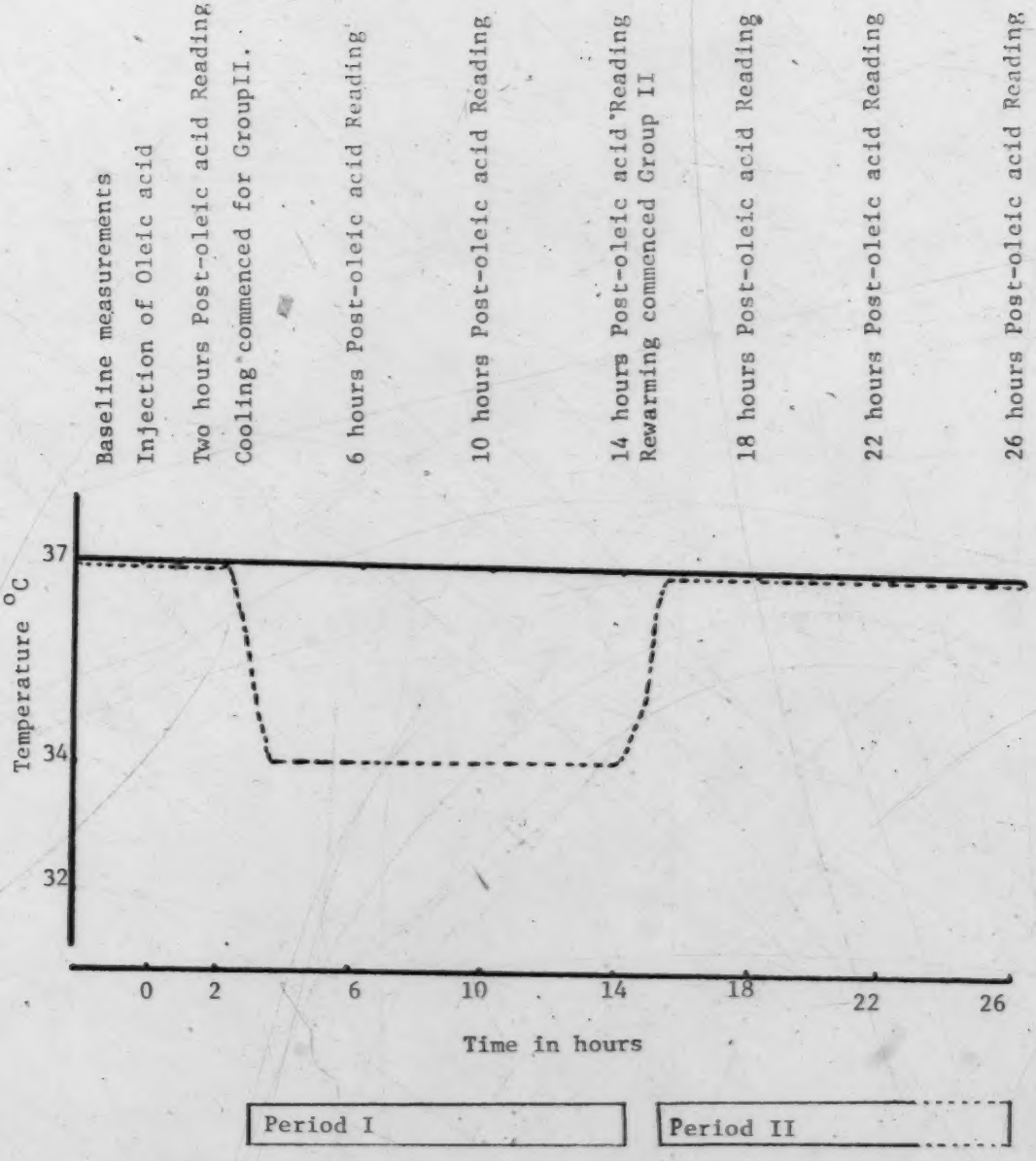

Figure 3. Time sequence of Readings and Periods I and II.
(Group I ——— , and Group II .....).

through a median sternotomy incision. The pleural cavities were examined and the heart and lungs removed en bloc subsequent to removal of endotracheal tube and severance of the trachea at mid-cervical level. The heart was examined for any obvious disease or damage and then separated from the lungs. The lungs were examined in detail and then inflated with a solution of 5% formaldehyde instilled into trachea through a Foley catheter with the balloon inflated. Lungs were kept inflated at a pressure of 30 cm water for 48 hours in a formaldehyde filled tank. Blocks of lung were obtained at random from different areas. These samples were embedded in paraffin, cut in sections of seven u thickness and stained with hematoxylin and eosin for histological examination. Four sections were examined from each lung.

An approximate grading of the histological pulmonary changes was made using a 30 point multipurpose grid and counting 900 points per section (at X450).

1. Interstitial edema 0 to 100% (mild to severe).
2. Alveolar edema 0 to 100%.
3. Capillary thrombosis and infarction.
4. Bronchopneumonia 0 to 100%, according to the distribution of inflammatory foci in the sections and actual counting of polymorphonuclear leucocytes.
5. Lung parenchyma 0 to 100%.
6. Extent of tissue necrosis.

E. Calculations (Adapted from Kao, 1974)

The following calculations were made from the data outlined above:

1. Arterial (CaO_2) and mixed venous ($C\bar{v}O_2$) oxygen content as volumes per cent at room air and 100% oxygen.

CaO_2 = (Hb x 1.34 x % O_2 saturation) + ($PaO_2 x \alpha$)

$C\bar{v}O_2$ = (Hb x 1.34 x % O_2 saturation) + ($PvO_2 x \alpha$)

where 1.34[1] is the amount of oxygen in ccs carried by one gram of hemoglobin when that gram is 100% saturated with oxygen; PaO_2 and $P\bar{v}O_2$ are oxygen partial pressures in arterial and venous blood and α is the solubility coefficient of oxygen in plasma. This varies at different body temperatures (Dittmer and Grebe, 1958).

2. Arterial and venous oxygen content difference (CaO_2 - $C\bar{v}O_2$) in volumes per cent.

3. Alveolar arterial oxygen partial pressure gradient ($A\text{-}aDO_2$) on room air and 100% oxygen. During room air breathing, to obtain $A\text{-}aDO_2$ the alveolar partial pressure of oxygen (PAO_2) needed was calculated by using the formula:

$$PAO_2 = PIO_2 - \frac{PaCO_2}{R} ;$$

where PIO_2 is the partial pressure of oxygen in inspired air (136 mmHg in Edmonton with barometric pressure of 700 mmHg); $PaCO_2$ is the partial pressure of carbon dioxide in the

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[1]There is still some controversy about this value. Some authorities give 1.36, 1.37, 1.39. But the majority use 1.34 since this is the actual amount of oxygen in ccs. given off from each gram of oxyhemoglobin when arterial blood is introduced into a Torricellian vacuum (Starling, 1912).

arterial blood; and R is the respiratory quotient obtained by dividing carbon dioxide production ($\dot{V}CO_2$) by oxygen consumption ($\dot{V}O_2$).

PAO_2 during 100% oxygen breathing was calculated by:

$$PAO_2 = PB - (PH_2O + PaCO_2)$$

taking barometric pressure as 700 mmHg in Edmonton and partial pressures of water corresponding to the animal's body temperature. This abbreviated equation for PAO_2 is used because during 100% oxygen breathing the only gases present in the alveoli are oxygen, carbon dioxide and water (nitrogen having been washed out).

4. True shunt expressed as a ratio of blood flow through unventilated regions ($\dot{Q}s$) versus cardiac output, or total flow ($\dot{Q}t$) and is derived from Berggren's equation (1941):

$$\frac{\dot{Q}s}{\dot{Q}t} = \frac{C\bar{c}O_2 - CaO_2}{C\bar{c}O_2 - CvO_2} \times 100$$

where $C\bar{c}O_2$ is the content of oxygen in the pulmonary capillary blood flowing through ventilated lung regions during 100% oxygen. In this blood hemoglobin oxygen saturation is assumed to be 100% and pulmonary capillay PO_2 is assumed to be equal to PAO_2.

$C\bar{c}O_2$ was obtained from:

$$(Hb \times 1.34 \times 1) + (PAO_2 \times \alpha)$$

In this case CaO_2 and $C\bar{v}O_2$ are the arterial and venous oxygen contents during 100% oxygen breathing.

5. Physiological dead space (V_D) was obtained by using the Bohr equation:

$$V_D = V_{T\ B.T.P.S.} \times \frac{PaCO_2 - PECO_2}{PaCO_2}$$

where V_T is the tidal volume expressed at body temperature, pressure and saturated with water vapour (BTPS).

6. Dynamic lung compliance = $\Delta V/\Delta P$ BTPS expressed as ml/cm water pressure, where V is the tidal volume (constant for each dog) expressed at BTPS and P is the tracheal pressure measured from the endotracheal tube.

7. Oxygen consumption ($\dot{V}O_2$)

$$= V_{STPD} \times FIO_2 \frac{FEN_2}{FIN_2} - FEO_2$$

8. Oxygen delivery was obtained from:

cardiac output x arterial oxygen content.

9. Cardiac output was also obtained by the Fick method i.e.:

$$\text{Cardiac output} = \frac{\text{Oxygen Consumption}}{\text{Arterio-venous oxygen difference}}$$

F. Statistical Analysis

Means, standard deviations and standard errors of the mean were calculated for all the parameters mentioned earlier. Using Fisher's unpaired and paired 't' tests, comparisions were made between Group I and Group II as well as within Group II between various observations during hypothermia and rewarming periods. Probability values $p<0.05$ were accepted as indicating significant differences.

CHAPTER III

Observations and Results

Each group comprised six dogs with mean weights 20.8±2.9 and 22.0±4.1 kgs for control (Group I) and hypothermic (Group II) respectively.

Baseline values for each of the variables for each animal were measured at their basal body temperature (37°C) and these values were used as controls for each dog. Baseline as well as subsequent results are plotted in Table I. However, values obtained two hours after the injection of oleic acid were expressed as a percentage of the initial baseline value (i.e., prior to the injection of oleic acid) for adequate comparison as to the extent of change in the two groups brought about by fat embolisation (Table II).

A. Oleic Acid Model

Oleic acid 0.075 ml/kg body wt. injected into the right ventricle produced a uniform response over the two hours initial observation period in both groups with a fall in PaO_2, pH, a rise in pulmonary artery pressure and a fall in the lung compliance (Table II) which was similar to that described in the previously reported experiments with this model (Ashbaugh and Uzawa, 1968; King et al, 1971). In view

TABLE I Experimental parameters measured for Group I and Group II. (Mean values ± S.D.)

S.No.	Parameter Studied	Group I						Group II						
		Pre Oleic Acid	2 hrs	6 hrs	10 hrs	14 hrs	18 hrs	22 hrs	Pre Oleic Acid	2 hrs	6 hrs	10 hrs	14 hrs	18 hrs	22 hrs
1	Hemoglobin gms%	15.6 ± 1.3	17.2 ± 0.7	17.7 ± 1.2	17.5 ± 1.3	18.0 ± 1.8	18.1 ± 1.9	18.3 ± 1.8	15.2 ± 0.72	17.8 ± 1.1	18.4 ± 1.3	19.1 ± 1.1	19.8 ± 1.3	19.9 ± 1.7	18.5 ± 1.4
2	Hematocrit %	42 ± 3	47 ± 3	48 ± 5	49 ± 5	51 ± 7	51 ± 8	52 ± 7	47 ± 5	54 ± 4	57 ± 4	59 ± 4	62 ± 6	67 ± 10	59 ± 5
3	PaO_2	83 ± 3	56 ± 12	59 ± 12	51 ± 9	53 ± 10	47 ± 9	44 ± 9	80 ± 4	50 ± 12	39 ± 6	40 ± 7	37 ± 9	38 ± 10	40 ± 12
4	$P\bar{v}O_2$	40 ± 4	32 ± 3	32 ± 5	33 ± 6	31 ± 6	30 ± 4	27 ± 3	41 ± 4	31 ± 8	25 ± 4	23 ± 6	25 ± 5	21 ± 8	27 ± 11
5	CaO_2	20 ± 2	20 ± 2	20 ± 2	19 ± 3	19 ± 3	17 ± 3	15 ± 3	20 ± 1	19 ± 4	19 ± 3	19 ± 4	18 ± 5	14 ± 6	14 ± 9
6	CaO_2-$C\bar{v}O_2$	5 ± 1	6 ± 1	7 ± 2	6 ± 2	7 ± 2	6 ± 1	7 ± 1	4 ± 1	6 ± 2	6 ± 1	8 ± 2	7 ± 2	8 ± 1	8 ± 2
7	A-aDO_2 (Room air)	24 ± 7	57 ± 10	50 ± 10	61 ± 11	56 ± 15	63 ± 11	55 ± 10	26 ± 7	55 ± 9	68 ± 15	64 ± 16	71 ± 13	57 ± 17	52 ± 20
8	A-aDO_2 (100% O_2)	143 ± 31	354 ± 136	372 ± 118	434 ± 124	470 ± 108	518 ± 79	526 ± 68	148 ± 30	461 ± 104	523 ± 90	539 ± 52	543 ± 46	553 ± 25	561 ± 24
9	pH arterial	7.48 ± 0.05	7.44 ± 0.06	7.42 ± 0.04	7.38 ± 0.05	7.36 ± 0.05	7.30 ± 0.13	7.22 ± 0.13	7.46 ± 0.03	7.4 ± 0.09	7.36 ± 0.08	7.32 ± 0.1	7.30 ± 0.12	7.10 ± 0.26	7.10 ± 0.3
10	pH venous	7.45 ± 0.04	7.39 ± 0.06	7.38 ± 0.04	7.34 ± 0.05	7.33 ± 0.05	7.27 ± 0.13	7.19 ± 0.14	7.43 ± 0.03	7.34 ± 0.1	7.34 ± 0.08	7.3 ± 0.11	7.24 ± 0.12	7.05 ± 0.3	7.00 ± 0.34

TABLE I (Cont.)

S.No. Parameter Studied	Group I						Group II						
	PreOleic Acid	2 hrs	6 hrs	10 hrs	14 hrs	18 hrs	22 hrs	PreOleic Acid	2 hrs	6 hrs	10 hrs	14 hrs	18 hrs	22 hrs
11 $\dot{Q}_S/\dot{Q}_T$ (Room air)	10 ± 3	33 ± 13	28 ± 11	42 ± 10	37 ± 13	47 ± 16	50 ± 18	13 ± 4	40 ± 19	48 ± 13	44 ± 9	57 ± 16	57 ± 14	61 ± 18
12 $\dot{Q}_S/\dot{Q}_T$ (100% O_2)	11 ± 2	16 ± 8	17 ± 6	21 ± 10	26 ± 17	41 ± 22	49 ± 17	11 ± 3	24 ± 11	36 ± 15	38 ± 20	33 ± 12	55 ± 17	44 ± 6
13 V_D (Physiol)	41 ± 8	41 ± 9	38 ± 9	36 ± 9	37 ± 14	40 ± 16	54 ± 12	42 ± 9	47 ± 10	42 ± 15	42 ± 18	45 ± 15	52 ± 30	51 ± 29
14 Compliance	49 ± 10	31 ± 13	27 ± 11	25 ± 11	23 ± 9	22 ± 5	19 ± 5	45 ± 15	30 ± 11	24 ± 10	23 ± 11	20 ± 12	23 ± 10	24 ± 10
15 Cardiac Output	3.08 ± 0.4	1.98 ± 1.01	2.14 ± 0.7	2.6 ± 1.1	2.3 ± 1.3	2.3 ± 1.3	2.3 ± 0.5	3.28 ± 0.8	2.4 ± 1.2	2.1 ± 0.9	1.8 ± 1.2	2.1 ± 1.2	1.96 ± 1.1	3.13 ± 1.02
16 Oxygen Delivery	6.22 ± 0.8	3.78 ± 1.65	4.33 ± 1.3	4.6 ± 1.5	4.4 ± 2.3	3.72 ± 1.9	2.93 ± 1.5	6.5 ± 1.8	4.86 ± 2.65	3.35 ± 1.9	3.77 ± 3.0	3.95 ± 3.0	3.85 ± 2.6	4.9 ± 3.7
17 Oxygen Consumption	152 ± 34	119 ± 41	142 ± 25	137 ± 35	139 ± 48	128 ± 47	146 ± 20	137 ± 32	135 ± 45	129 ± 72	128 ± 56	119 ± 75	134 ± 76	156 ± 91
18 Heart Rate	194 ± 34	175 ± 24	163 ± 32	170 ± 43	165 ± 47	149 ± 41	134 ± 52	194 ± 30	185 ± 29	164 ± 37	142 ± 17	146 ± 24	172 ± 6	158 ± 62
19 Mean Systemic Art. Pressure	139 ± 17	129 ± 17	133 ± 17	128 ± 26	117 ± 20	106 ± 27	95 ± 26	143 ± 8	137 ± 15	135 ± 15	134 ± 12	128 ± 13	101 ± 36	102 ± 50
20 Mean Pulmonary Art. Pressure	10 ± 1	14 ± 3	21 ± 5	21 ± 5	21 ± 5	21 ± 4	23 ± 3	9 ± 2	13 ± 4	16 ± 3	19 ± 5	19 ± 3	17 ± 5	18 ± 4

Table II. Experimental values (means and Standard Deviations) obtained two hours after the injection of oleic acid, expressed as percentages of baseline values.

S.No	Parameter measured	Group I Control (Normothermia)	Group II (Normothermia) at this stage
1.	Hemoglobin	110 ± 6	118 ± 9
2.	Hematocrit	114 ± 9	115 ± 11
3.	PaO_2 (room air)	67 ± 13	63 ± 17
4.	$P\bar{v}O_2$ (room air)	82 ± 11	75 ± 15
5.	CaO_2 (room air)	98 ± 4	97 ± 16
6.	$CaO_2-C\bar{v}O_2$ (room air)	134 ± 40	134 ± 32
7.	$A-aDO_2$ (room air)	263 ± 69	230 ± 81
8.	$A-aDO_2$ (100% O_2)	252 ± 84	328 ±120
9.	pH arterial	99 ± 0.5	99 ± 1
10.	pH venous	99 ± 0.5	99 ± 1
11.	$\dot{Q}s/\dot{Q}t$ (room air)	338 ±142	377 ±314
12.	$\bar{Q}s/\bar{Q}t$ (100% O_2)	144 ± 84	248 ±176
13.	Physiol. Dead Space	98 ± 16	116 ± 37
14.	Effective Compliance	63 ± 17	66 ± 17
15.	Cardiac Output	64 ± 30	69 ± 21
16.	Oxygen Delivery	62 ± 27	72 ± 31
17.	Oxygen Consumption	82 ± 35	97 ± 14
18.	Heart Rate	91 ± 11	96 ± 16
19.	Systemic Arterial Pressure	93 ± 6	95 ± 6
20.	Pulmonary Artery Pressure	143 ± 32	138 ± 31

of the consistently obtainable changes with this experimental model reported in the literature it was considered appropriate to use only one set of post-oleic acid measurements to represent alterations due to fat embolisation.

All the dogs became hypotensive with a fall in heart rate and cardiac output. There was a marked elevation (300-377%) in the alveolar-aterial oxygen gradients both at room air as well as while breathing 100% oxygen. Venous admixture and absolute shunt also increased proportionately signifying the degree of pulmonary damage which resulted in profound alterations in ventilation and perfusion balance. A 10-17% increase in hemoglobin and hematocrit concentrations probably represented sequestration of some of the intravascular volume in the lungs. Tracheal secretions became frothy, profuse and hemorrhagic requiring frequent endotracheal suctioning. All these changes are akin to the ones observed in the clinical ARDS. Hence this clinical surrogate served as an adequate experimental model for further studies in the two groups.

From Tables I and II it becomes apparent that although all the parameters became altered in the two groups, some did so more in one than in the other and vice versa. Hemoglobin, hematocrit, pH, lung compliance, heart rate, systemic and pulmonary artery pressures showed a similar degree of change in the two groups two hours after injection

of the oleic acid. In contrast, cardiac output, venous admixture, absolute shunt, dead space ventilation and the alveolo-arterial gradients for oxygen were different in the two groups. In view of this difference (though these were not statistically significant at $p<0.05$) further observations as regards hemoglobin, hematocrit, pH, heart rate, systemic and pulmonary artery pressure as well as lung compliance were expressed as percentage of the baseline values (i.e., before the injection of oleic acid), since there was no appreciable difference in the two groups initially or subsequently (Table III).

As the oleic acid-induced ARDS model became established, changes in arterial oxygenation, and oxygen transport and utilization became obvious in the two groups. In order to study the degree of change brought about by hypothermia and subsequent rewarming in Group II dogs, it was decided to analyze the observations obtained during these periods and compare the same with each other and with the corresponding periods in Group I. These periods were: a) Period I - normothermia for Group I and hypothermia for Group II and b) Period II - normothermia for Group I and normothermia following rewarming for Group II. It is clear that whatever changes took place, these happened with regard to the post-oleic acid values. Thus the results obtained during Period I and Period II for the two groups were expressed as percentages of the values obtained at two hours after oleic acid injection for proper normalization and

TABLE III Experimental parameters measured for Group I and Group II. Values expressed as percentages of the baseline values.

S.No.	Parameter Studied	Group I PreOleic Acid	2 hrs	6 hrs	10 hrs	14 hrs	18 hrs	22 hrs	Group II PreOleic Acid	2 hrs	6 hrs	10 hrs	14 hrs	18 hrs	22 hrs
1	Hemoglobin	100	110 ± 6	114 ± 11	112 ± 11	115 ± 11	116 ± 12	117 ± 12	100	118 ± 9	121 ± 7	125 ± 5	131 ± 6	131 ± 6	122 ± 11
2	Hematocrit	100	115 ± 9	115 ± 9	117 ± 13	120 ± 13	120 ± 13	123 ± 13	100	115 ± 11	121 ± 8	126 ± 11	133 ± 8	142 ± 12	126 ± 17
3	pH Arterial	100	99 ± 0.5	99 ± 0.5	99 ± 1	97 ± 1	96 ± 2	98 ± 0.0	100	99 ± 1	99 ± 1	98 ± 2	98 ± 2	96 ± 4	96 ± 4
4	pH Venous	100	99 ± 0.5	99 ± 0.5	99 ± 0.5	98 ± 0.5	98 ± 2	96 ± 2	100	99 ± 1	99 ± 1	98 ± 2	97 ± 2	96 ± 4	96 ± 4
5	'Effective' Compliance	100	63 ± 17	55 ± 13	51 ± 15	47 ± 11	46 ± 8	40 ± 11	100	66 ± 17	52 ± 12	49 ± 13	46 ± 13	52 ± 8	51 ± 5
6	Heart Rate	100	91 ± 11	84 ± 5	89 ± 24	86 ± 26	79 ± 26	70 ± 25	100	96 ± 16	85 ± 15	80 ± 9	80 ± 17	92 ± 10	82 ± 36
7	Systemic Artery Pressure	100	93 ± 6	96 ± 14	92 ± 17	85 ± 17	78 ± 21	70 ± 23	100	95 ± 6	94 ± 7	94 ± 10	90 ± 13	72 ± 29	74 ± 37
8	Pulmonary Artery Pressure	100	143 ± 32	218 ± 46	215 ± 47	217 ± 55	231 ± 43	233 ± 40	100	138 ± 31	171 ± 30	202 ± 22	214 ± 28	197 ± 43	209 ± 8

adequate comparison (Table IV).

B. Results

Hemoglobin and hematocrit (Fig. 4) showed a slow increasing trend in both groups during the entire experiment although the most marked changes had taken place immediately after fatty acid injection. Similarly heart rate and systemic arterial pressures fell in both groups. These changes were similar for both groups and no statistically significant differences were seen between the observation periods. A progressive fall in heart rate was followed by increasing atrioventricular conduction block which led to bradycardia and terminally ventricular fibrillation and asystole. At this stage, these dogs showed marked hypoxemia and metabolic as well as respiratory acidosis with elevated arterial pCO_2 in the region of 54-64 mmHg. Figure 5 shows changes in the arterial pH which were more or less similar in the two groups and represent deteriorating acidosis. Arterial pH fell further in Group II when the dogs were rewarmed following their 12 hour period of hypothermic observation. Although these results were not statistically different the fall in pH (7.1 as compared to 7.32 during hypothermia) represents perhaps a biologically 'significant' increase in acidosis in the light of other findings at this stage. Lung compliance, monitored as change in airway pressure over the fixed tidal volume, showed progressive,

Table IV. Measurements of variables in the two groups at Period I and Period II (expressed as percentage of two hours post-oleic acid values).

S. No.	Measurement	Group I			Group II		
		2 hrs after O.Acid	Period I	Period II	2 hrs after O.Acid	Period I	Period II
1	PaO_2 (room air)	100	99 ± 12	87 ± 22	100	82 ± 15	73 ± 18
2	$P\bar{v}O_2$ (room air)	100	100 ± 13	93 ± 17	100	81 ± 19	65 ± 23
3	CaO_2 (room air)	100	101 ± 6	89 ± 21	100	98 ± 9	69 ± 27
4	$CaO_2-C\bar{v}O_2$ (room air)	100	104 ± 18	100 ± 20	100	130 ± 6	174 ± 128
5	$A-aDO_2$ (room air)	100	94 ± 11	107 ± 13	100	140 ± 27	111 ± 30
6	$A-aDO_2$ (100% O_2)	100	128 ± 37	166 ± 69	100	118 ± 18	126 ± 27
7	Q_S/Q_T (room air)	100	123 ± 107	165 ± 101	100	143 ± 48	187 ± 114
8	Q_S/Q_T (100% O_2)	100	141 ± 45	292 ± 181	100	171 ± 81	267 ± 23
9	V_D (Physiol.)	100	91 ± 16	99 ± 26	100	85 ± 22	126 ± 88
10	Cardiac Output	100	128 ± 45	119 ± 53	100	83 ± 44	83 ± 45
11	Oxygen Transport	100	124 ± 43	96 ± 23	100	84 ± 50	75 ± 44
12	Oxygen Consump.	100	123 ± 34	89 ± 26	100	96 ± 33	89 ± 28

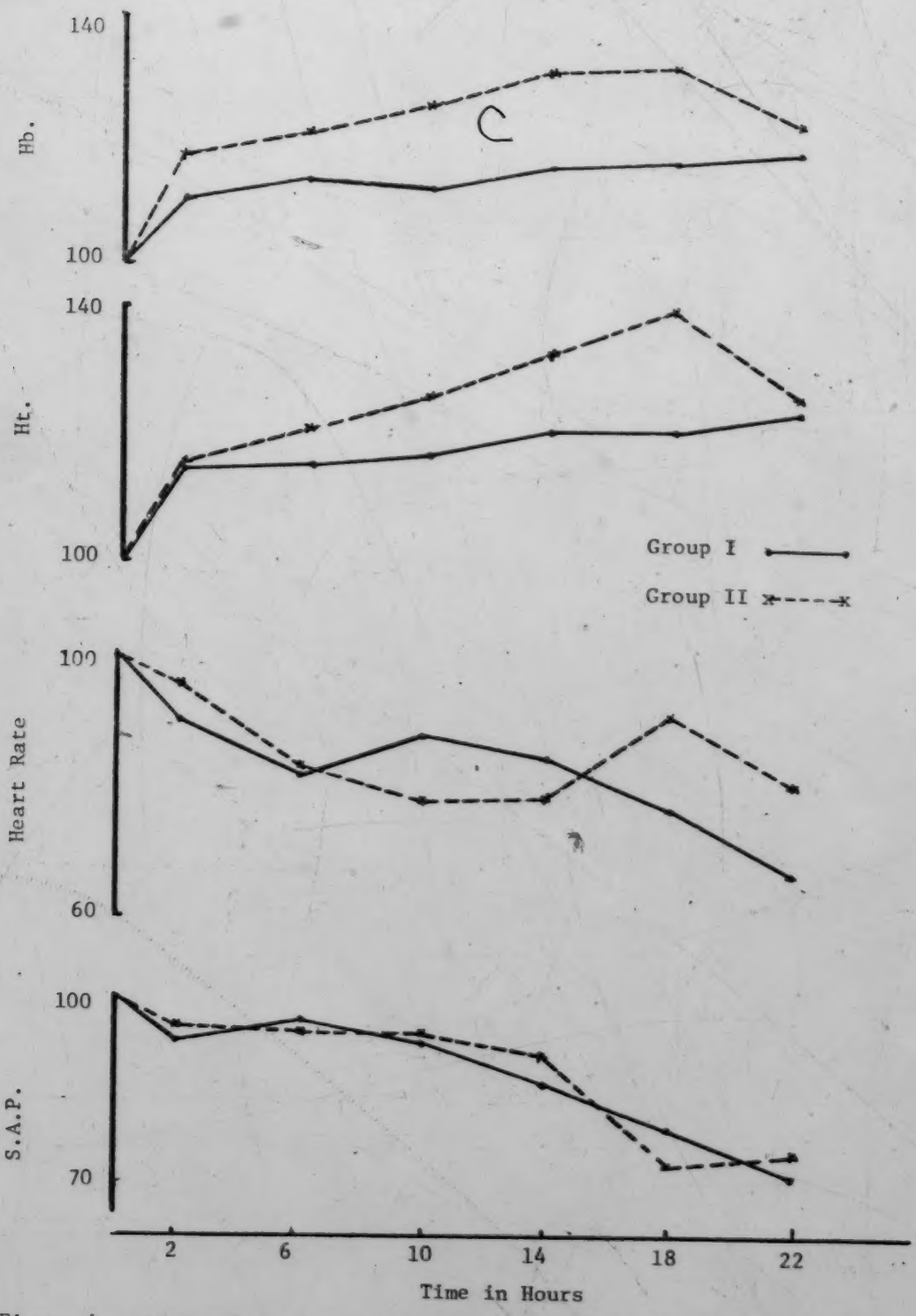

Figure 4 Mean values for hemoglobin, hematocrit, heart rate and systemic artery pressures (S.A.P.) for groups I and II expressed as percentages of pre-oleic acid controls.

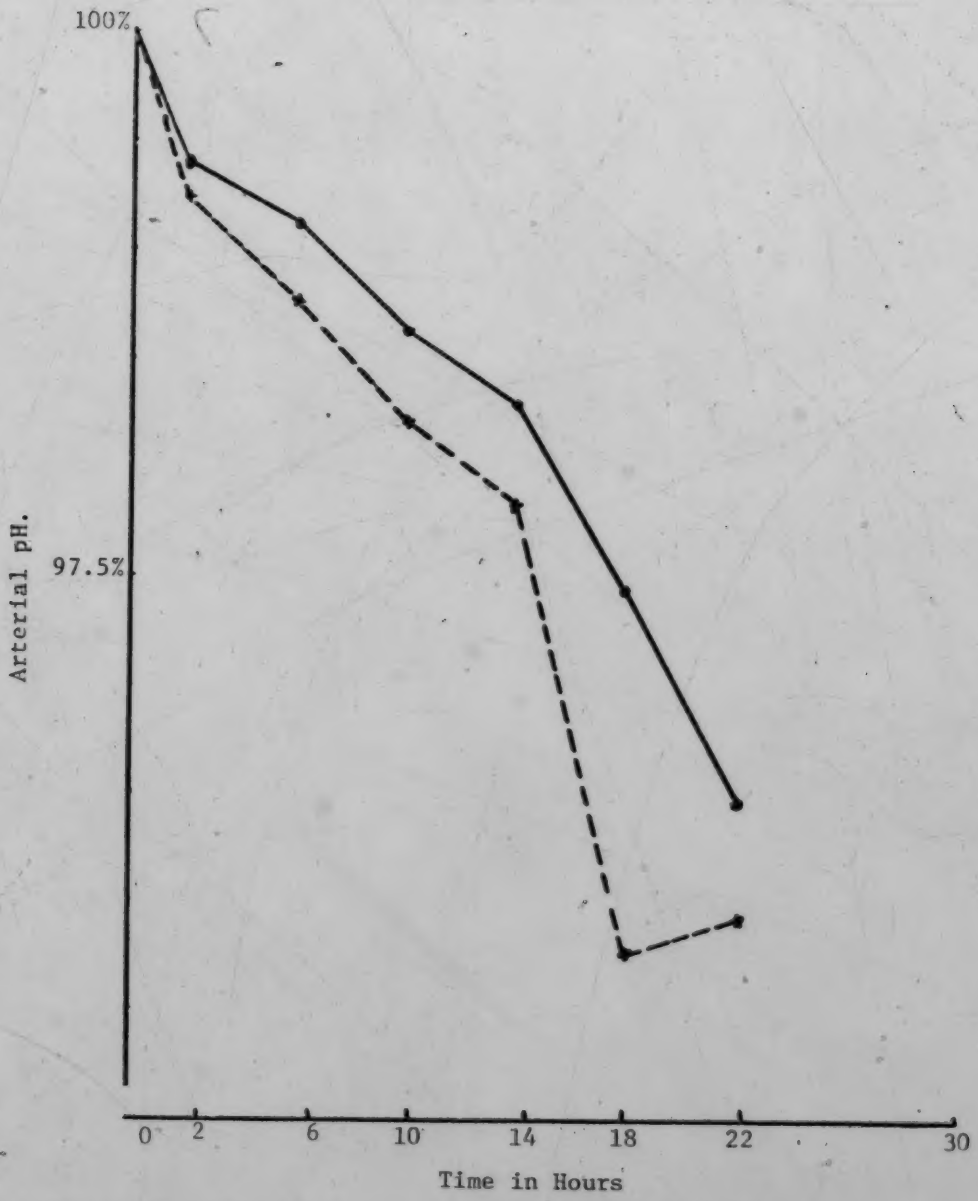

Figure 5 Changes in arterial pH in the two groups: Group I ●——●, Group II ✱- - - -✱ (Mean values expressed as percentages of the baseline pre oleic acid values)

although slow, deterioration after the initial drastic reduction observed at two hour period following the injection of oleic acid. The magnitude of this change was of the same order in both groups. Airway pressures rose as the lungs became stiff with a consequent fall in lung compliance (Fig. 6). Pulmonary artery pressure increased with the fall in compliance. Hypothermia, as well as rewarming, did not alter the changes in lung compliance and pulmonary artery pressures to a statistically significant degree.

Ventilation-Perfusion Mismatch

Ventilation-perfusion mismatch as represented by widened A-aDO_2, venous admixture and total shunt as well as dead space ventilation worsened as the experiment progressed (Fig. 7 and 8) indicating an increase in the pulmonary parenchymal damage. The A-aDO_2 increase in Group II was greater during the hypothermia period as compared to Group I ($p<0.001$). This may represent an increased diffusion defect or ventilation-perfusion mismatching during hypothermia which was partially corrected while breathing 100% oxygen so that the rise in the alveolar arterial oxygen gradient was less steep than the one observed breathing room air. During rewarming, increase in A-aDO_2 kept pace with the increase in venous admixture and absolute shunt which did not show any significant differences in the two groups. Physiological dead space ventilation decreased to some extent in the two groups, perhaps, with controlled intermittent positive

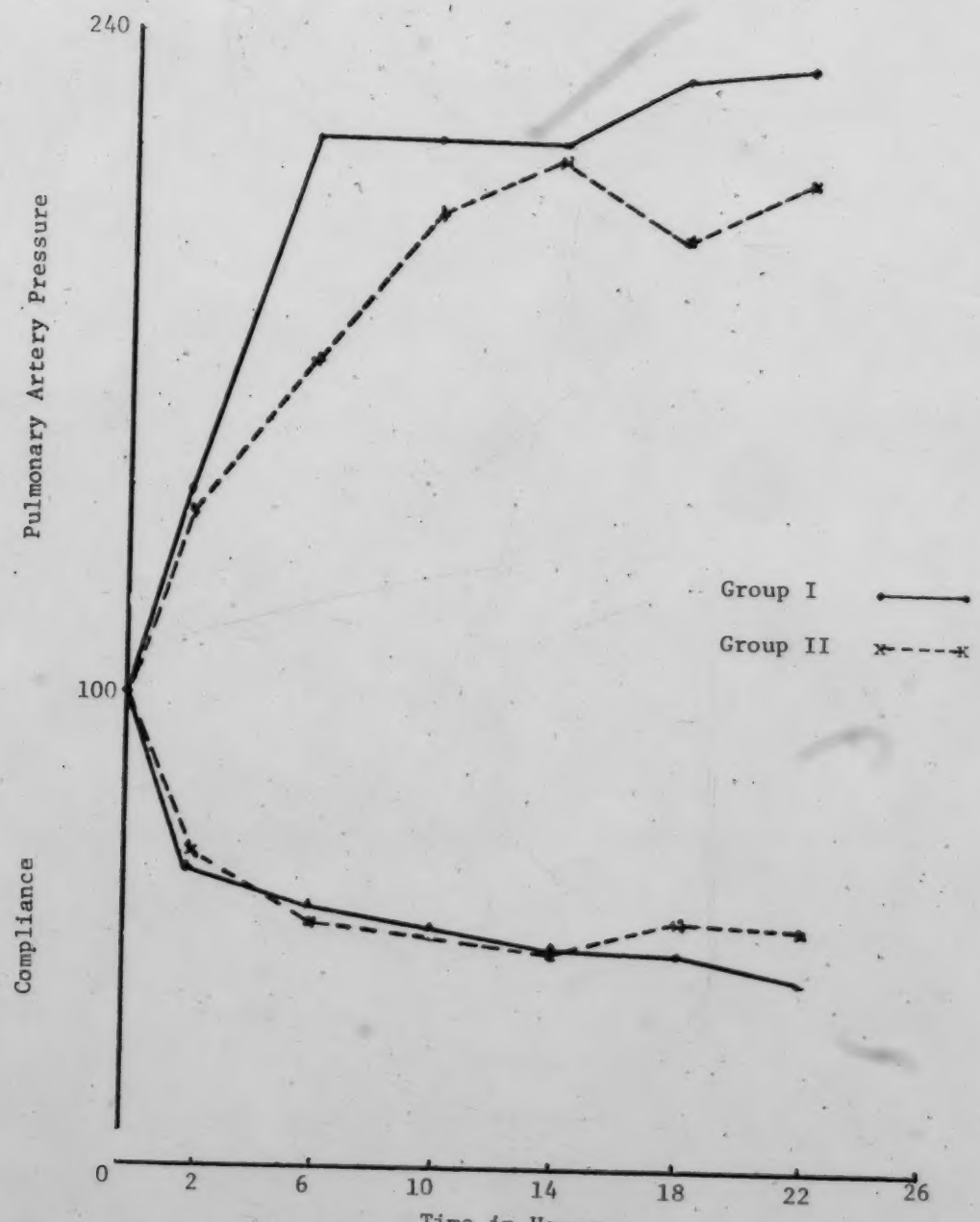

Figure 6 Changes in pulmonary artery pressure and Dynamic lung compliance expressed as percentages of the pre-oleic acid baseline values.

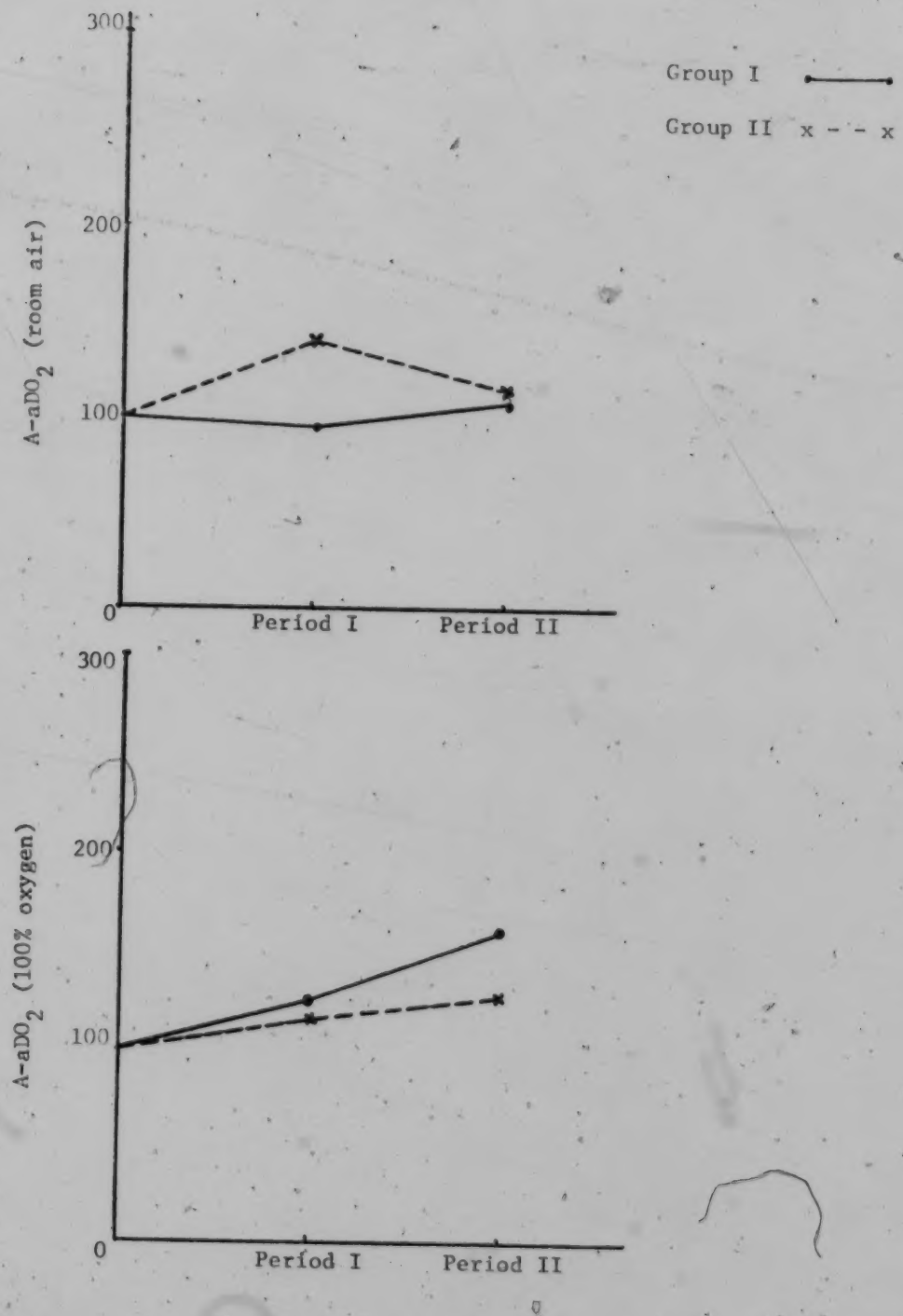

Figure 7 $A\text{-}aDO_2$ with room air and 100% oxygen.
Period I: Normothermia in Group I and Hypothermia in Group II
Period II: Normothermia in Group I and rewarming in Group II

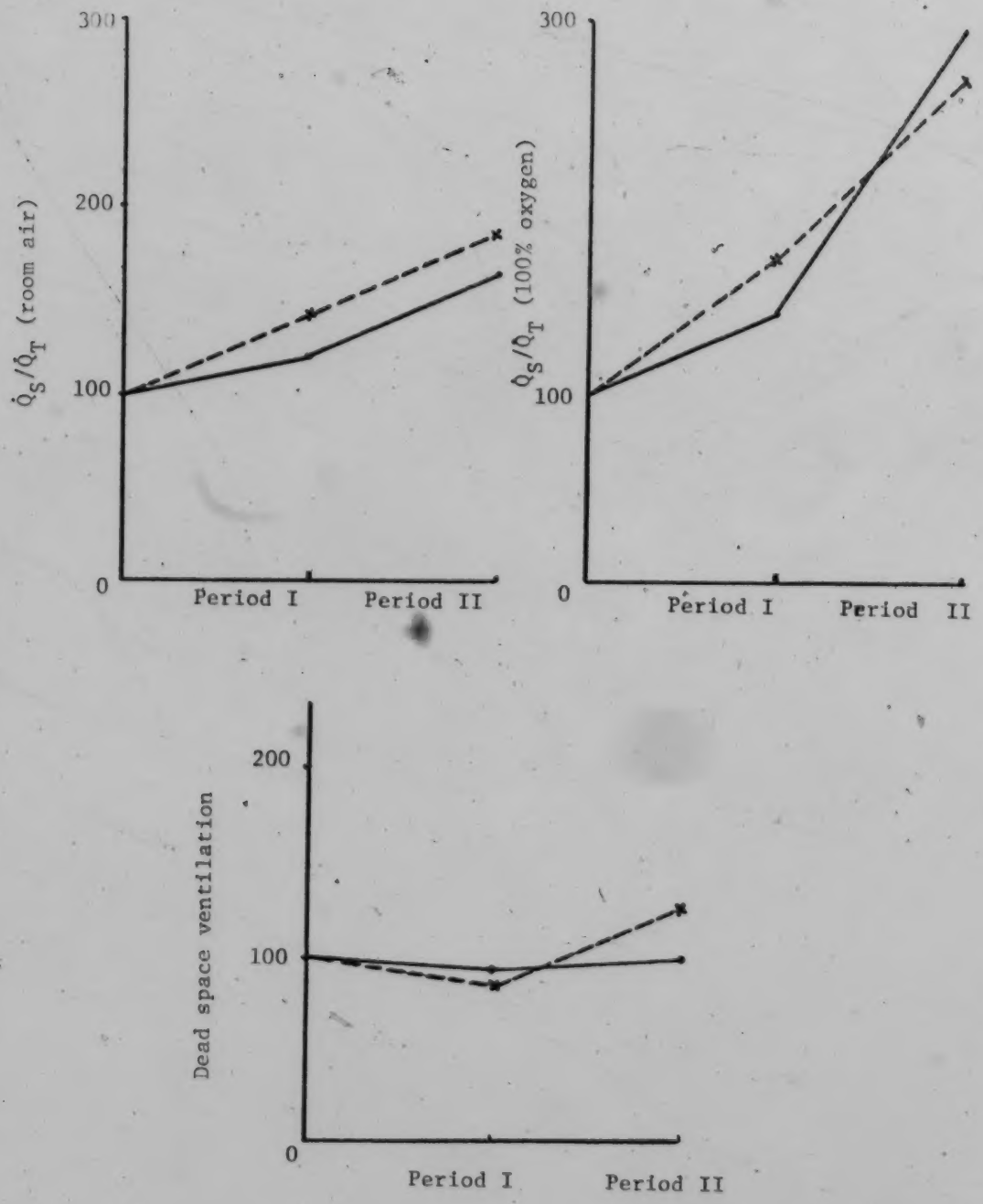

Figure 8 Calculated venous admixture; absolute shunt and physiological dead space ventilation in Group I ——— and Group II *----*. Results are mean values expressed as percentage of the post oleic acid values.

pressure ventilation. However, rewarming in Group II was followed by an increase in dead space ventilation from 86% during hypothermia period to 126% after normothermia was restored. This change was statistically significant at $p<0.05$.

Oxygenation of Blood

Oxygenation of blood as indicated by alterations in PaO_2, $P\bar{v}O_2$, oxygen contents and saturation showed the most obvious changes (Fig. 9). While PaO_2 remained fairly stable in the control group, it decreased significantly in Group II during hypothermia as well as upon rewarming. $P\bar{v}O_2$ also showed a statistically significant decrease with hypothermia becoming worse with rewarming as compared to the normothermic controls. Arterio-venous oxygen content difference increased significantly with hypothermia which persisted during rewarming (Fig. 10). Arterial oxygen content in the two groups did not show any significant changes until the rewarming in Group II when it fell slightly.

Oxygen Transport and Consumption

Upon injection of oleic acid, cardiac output decreased in both groups. Cardiac output returned to pre-injection values in the control group (Group I) suggesting no further abnormalities in cardiovascular functions during normothermia (Fig. 11). However, cardiac output decreased

Figure 9 Arterial and venous oxygen tension in Group I ●——● and Group II x - - x during the two observation periods. Values expressed as percentages of the 2 hour post oleic acid values.

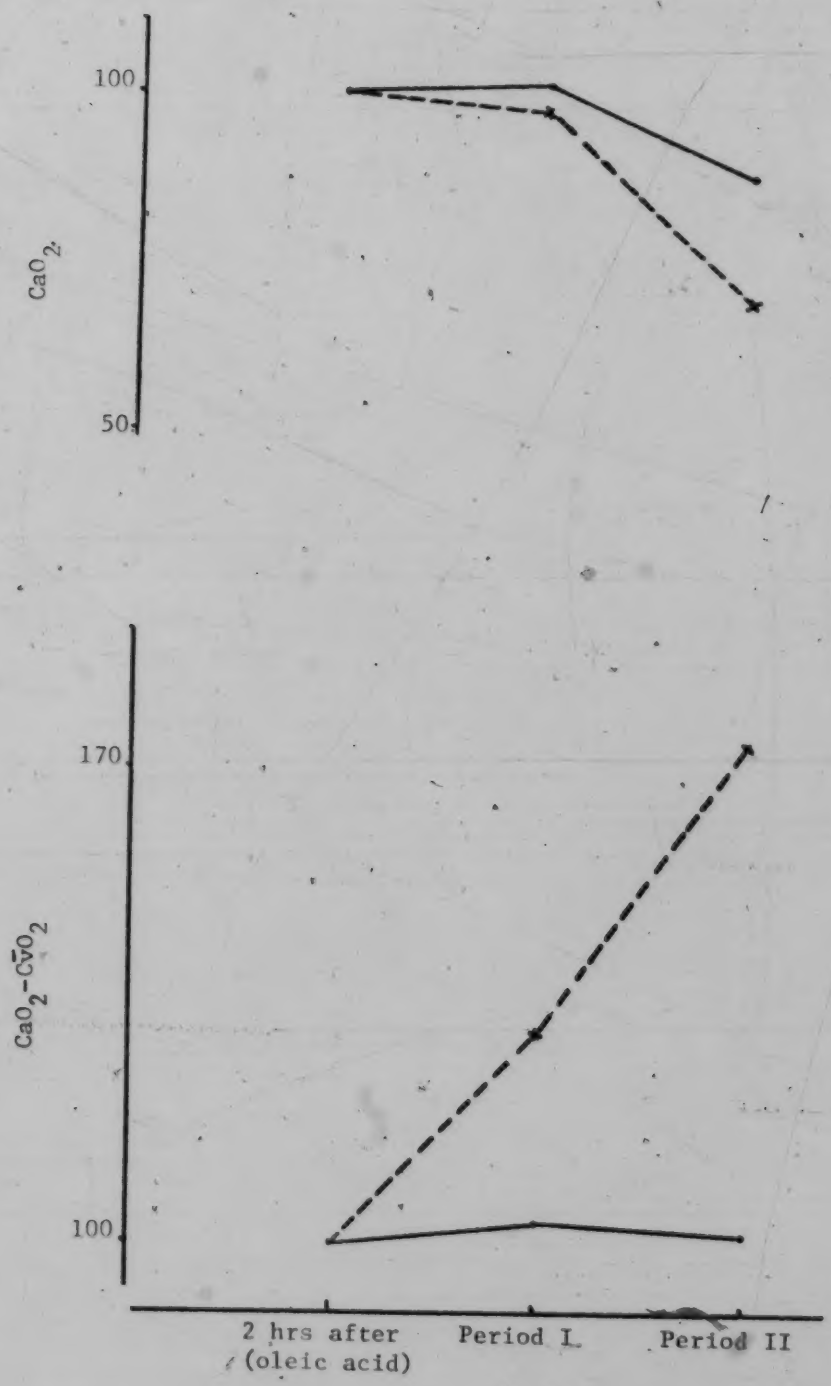

Figure 10 Alterations in arterial oxygen content and arterio-venous oxygen content difference. Group I: ——— (control) Group II x - - x

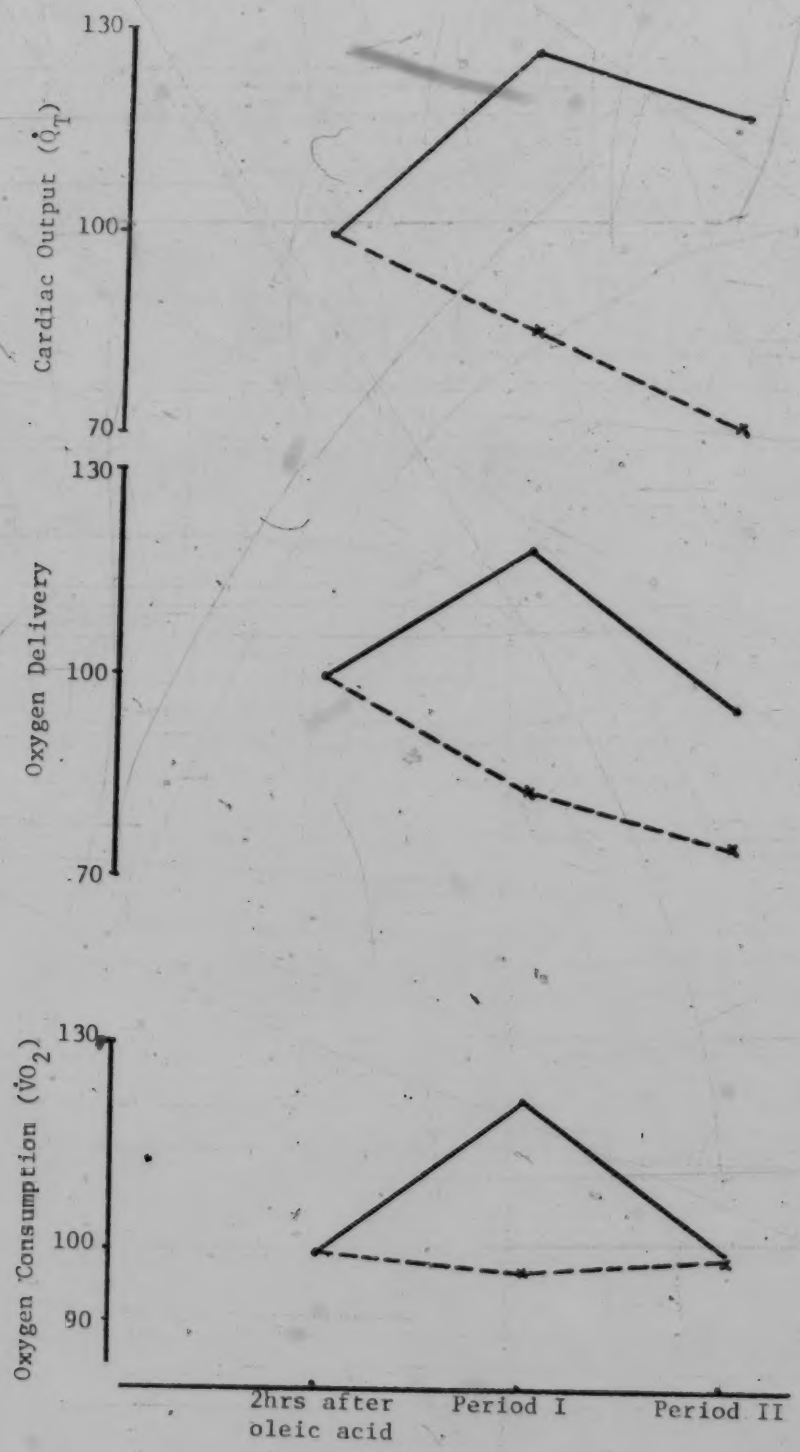

Figure 11 Changes in cardiac output (Q_T), oxygen delivery and oxygen consumption (VO_2) in group I ——— and Group II x - - x

further with the induction of hypothermia in Group II and remained below "normal" levels even after rewarming. The drop in cardiac output and the decrease in arterial oxygen content resulted in a decreased oxygen transport to the tissues during hypothermia as well as during rewarming (Fig. 11) in sharp contrast to the control group where oxygen delivery tended to improve or at least keep pace with the increase in oxygen consumption. As expected, oxygen consumption did fall during hypothermia. The decrease in oxygen consumption was significant as compared to the Group I where the oxygen consumption had increased (Fig. 11). Oxygen consumption, however, decreased in Group I during the second twelve hour observation period (Period II).

Survival Curves

Fig. 12 summarises the survival of dogs in the two groups. Four dogs in Group I died of bilateral pneumothoraces between 22 and 26 hour observation period. This may be of significance as none of the dogs in Group II developed pneumothorax. There were two survivors in each group up to the 26 hour observation period. Four dogs died during the experiment in Group II, one during hypothermia of profound hypoxemia and hypercapnea (PaO_2-26 mmHg, $PaCO_2$-64 mmHg) and three after rewarming, again due to hypoxemia and acidosis (pH<7.00).

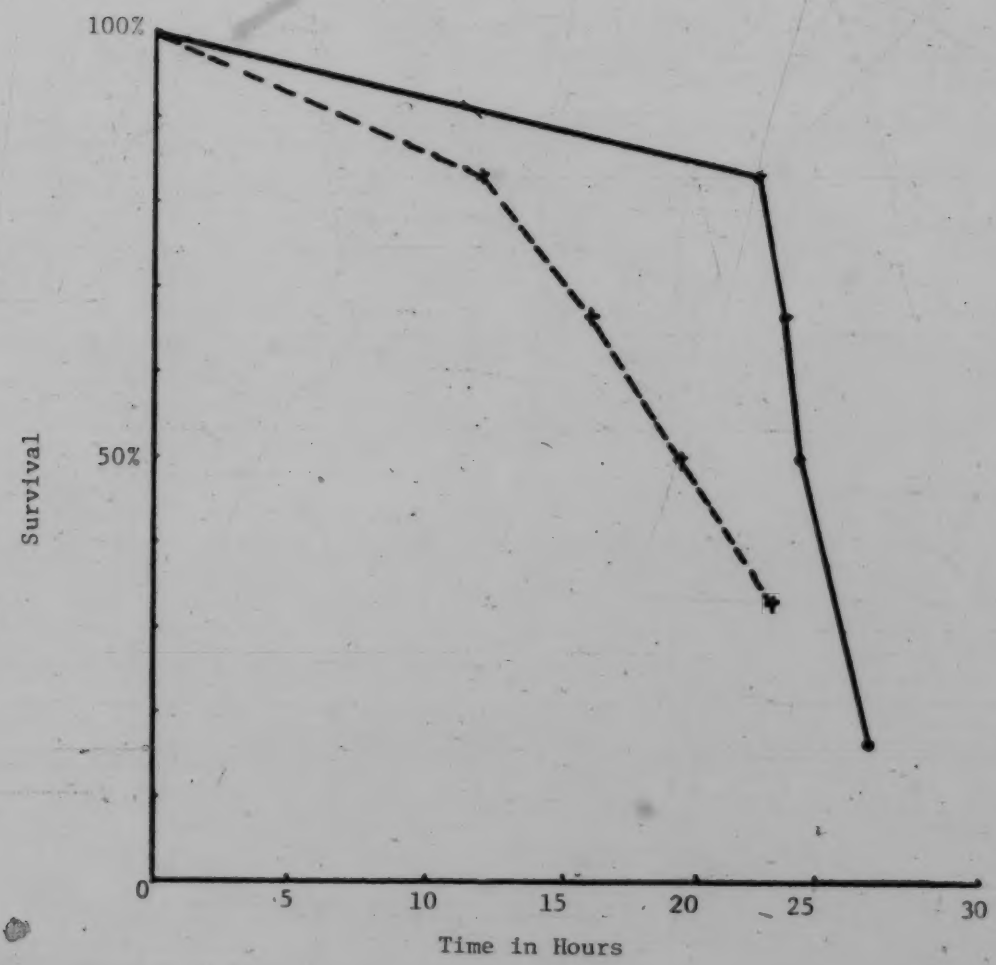

Figure 12 Survival period in the two groups, Group I ——— and Group II x - - x, expressed as percentage survival of the total.

Pathological Examination

The pathological-anatomical changes were of the same nature for both groups. Postmortem examination, carried out at the end of each experiment, revealed bilateral hemorrhagic pleural effusions in all dogs: the volume of the effusion varied between 200 ml to 350 ml. The lungs were diffusely mottled, dark red in color with some blue blotchy patches and areas of frank hemorrhage. The lungs were homogenously involved with hemorrhagic edema (Fig. 13) with changes observed both anteriorly and posteriorly. The airways were full of frothy hemorrhagic secretions which extended into the endotracheal tube. The lungs were heavy and non-crepitant. The heart and diaphragm appeared normal. One dog in Group II developed melena during the course of the experiment and at autopsy diffuse edematous hemorrhagic patches were visible in the stomach and proximal duodenum.

Microscopic Examination

The microscopic examination of lungs revealed similar changes in both groups with alveolar and interstitial edema, capillary congestion, diapedesis of erythrocytes and increased cellularity. Thrombi were visible in the pulmonary arterioles with areas of infarction surrounding these areas. Thrombosis and infarction were more marked in hypothermic dogs as compared to control dogs. There was a significant infiltration with leucocytes either spread diffusely or in localised areas suggesting frank pneumonia and consolidation

Figure 13 Macroscopic appearances of lungs before (top) and after the injection of Oleic acid (bottom).

in these lungs (Fig. 14a). Cellular infiltration was statistically significant ($p<0.005$) in the control dogs suggesting an increased incidence of pneumonia in these dogs (Fig. 14b). The reason for the pneumonic changes may be the observation that control dogs survived longer as compared to the hypothermic dogs and thus had more time to develop signs of infection. There was a mild to moderate interstitial edema in many of the tissue sections. Hyaline membranes were not seen in either group. Few of the sections showed no pathologic abnormality in both groups.

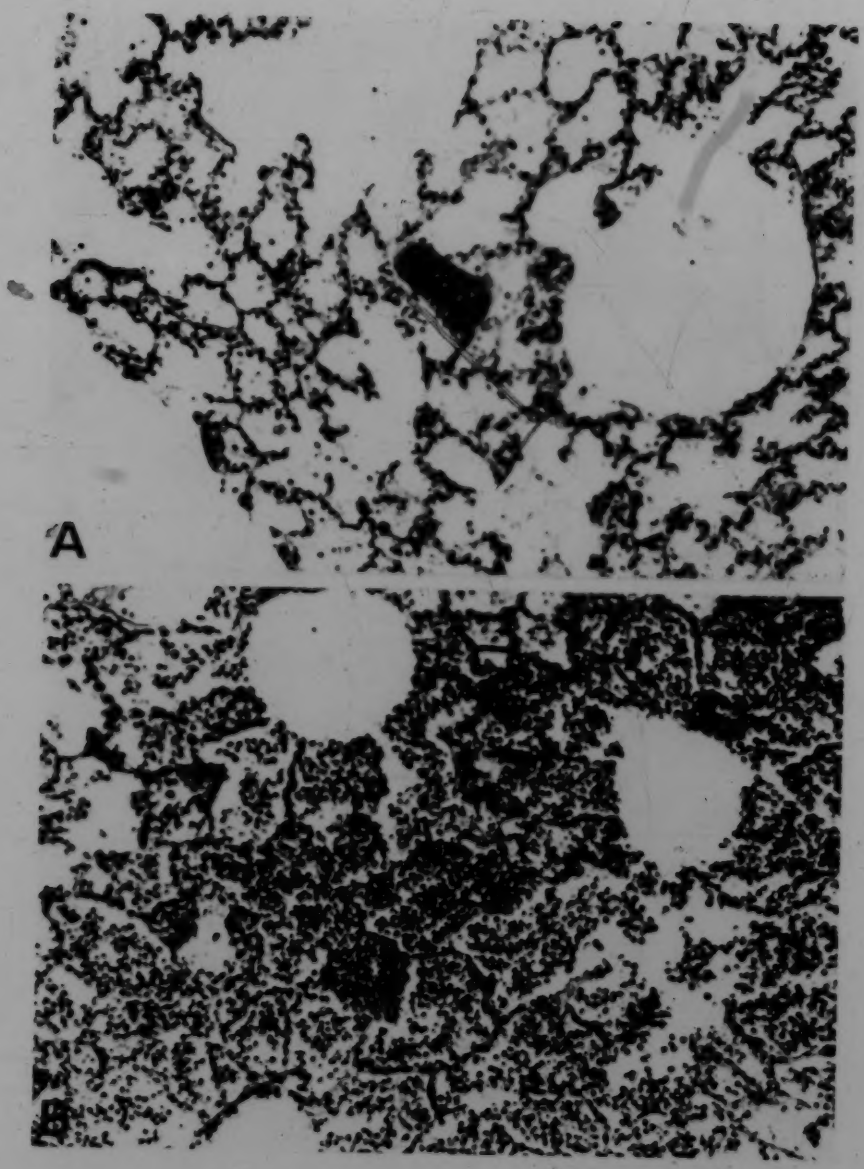

Figure 14
Photomicrograph of Group II dog lung showing thrombosis, cellular infiltration and tissue destruction (top), and pronounced leucocytic infiltration and pneumonic consolidation in Group I dog lung (bottom)
(H&E stain, x 120)

CHAPTER 4

Discussion

The principle behind the clinical use of induced hypothermia is to reduce the metabolic rate so as to create a more favorable balance between oxygen supply and demand (Halmagyi et al, 1973). Although survival has been reported in dogs cooled to as low as 1.5°C (Gollan et al, 1955) it is only in the temperature range of 32-35°C that hypothermia has been found safe, easily controllable and most useful in clinical practice. At this temperature range, there are no abnormal changes in myocardial contractility, nor are there any documented histo-chemical changes in the organ ultrastructure (Fisher et al, 1957; Rittenhouse et al, 1972). Besides, it is free from the complication of "after drop" and does not seem to interfere with the milieu intereur of the body in that there are no obvious fluid or electrolyte disturbances.

Hypothermia has been advocated in the management of acute pulmonary hypoxia (Swan, 1973). The rationale for its use in pulmonary problems centers around hypoxia which is often progressive despite adequate treatment. With regard to the pulmonary system, the deficit would mainly reside with inability of the lungs to maintain an adequate systemic arterial oxygen tension and to get rid of carbon dioxide

from the body. The hypoxic situation would, theoretically be ameliorated by using hypothermia because of the reduction in oxygen demands. Hopefully, the benefits accrued would be twofold. First, the body would be brought more in line with oxygen procurement within the limits of lung abilities, reduced that these are. Second, by reduction of oxygen requirements, the work expected of the oxygen delivery system would be decreased with reduction in stress response (Blair, 1964). To be of full benefit to the general body functions, it should not be detrimental to pulmonary structure and function. That this is so has already been shown in normal situations by the observations of Talbot, (1941) and Blair, (1964). Oxygen transport and consumption has been studied in healthy dogs and other animals both during hypothermia and rewarming. With the lowering of body temperature in normal human beings and animals, there is a proportionate fall in oxygen consumption and its transport since cardiac output falls at the same time. How, then, does hypothermia restore the balance between oxygen supply and demand? Recently Mohri et al, 1974 showed, in uniformly cooled dogs, that as the body temperature was lowered, oxygen consumption and oxygen delivery decreased but the former decreased much more than the latter (Fig. 1). In contrast, Kent and Converse - Pierce II (1974) showed that the reverse was true. Swan (1956) reported that during cooling, there was a linear relationship between cardiac output and oxygen consumption and hence the cardiac output,

decreased as it may be, was sufficient for the oxygen requirements of tissues. However, this relationship was altered upon rewarming when the cardiac output did not match with the now increased requirements of the body. This is especially true in view of the oxygen debt that is incurred during hypothermia (Dieter and Neville, 1972).

Hypothermia has been recommended in hypoxic states such as shock syndromes. In fact, it is being used almost routinely in some Intensive Care Units. Is it useful and if so, what is the rationale for its use? Obviously the mechanism of oxygen transfer and its utilization in the body during hypothermia is far from clear and confusion still exists regarding these two functions even in normal controlled situations (Mohri et al, 1974). It is possible, amidst this confusion, that hypothermia may in fact, be detrimental (Bryan-Brown, 1973).

An entirely different and precarious situation exists in critically ill and hypoxemic patients. These patients are existing with severely compromised cardio-respiratory functions and any factor or factors that interfere with oxygen uptake and utilization in the tissues would tilt the balance against the patient. Further McConn and her colleagues (1971) have shown that oxygen affinity of hemoglobin can change in acute disease. There is a shift of the oxygen-dissociation curve to the left and this occurs directly as a result of the disease state itself. This left shift of the oxygen-dissociation curve may worsen with

hypothermia which causes further shift to the left (Severinghaus, 1959) which would severely impair the transfer of oxygen from blood to tissues. With this background, the present study was carried out to determine how oxygen transport and oxygen utilization are influenced by hypothemia during acute hypoxemic respiratory failures.

Oleic Acid Model

Patho-physoliogical alterations occuring in the Adult Respiratory Distress Syndrome have been experimentally reproduced in various animal models. Some of these models have been produced by hemorrhage, alloxan, prolonged bypass, shock following lower limb ischemia and oleic acid injection. Pulmonary structure and function is minimally altered in some of these (Hillen et al, 1971) and the changes that do take place are delayed and usually not consistent (Garvey et al, 1975). The oleic acid induced ARDS model was first described by Ashbaugh and Uzawa (1968). Oleic acid produces profound hypoxemia similar to that described in pulmonary fat embolism by Sproule and his colleagues, (1964). This model was devised to study the nature of changes and therapeutic implications in an experimental situation that exhibited all the clinical, pathological and physiological features of the ARDS. Selective administration of oleic acid into the pulmonary circulation produces severe respiratory distress with minimal hemodynamic changes. That this is true is shown by

the observation that cardiac output, after an initial drop, is restored to normal or even above normal values within one hour of the injection (Ashbaugh and Uzawa, 1968). However the increase in cardiac output is accompanied by a pronounced fall in arterial oxygen tension, a decrease in lung compliance and an increase in pulmonary artery pressure. The present study demonstrated (Table I) a marked fall in lung compliance, arterial hypoxemia and an increase in ventilation-perfusion mismatch similar to those reported by King et al (1971) and Jones and King (1975). These changes were consistently reproducible in all the experimental studies. There is an increase in the capillary permeability resulting in a 'leaky vessel syndrome' (Teplitz 1968; King et al, 1971) which leads to catastrophic hypoxemia culminating in death of the animal within three to five hours if not artificially ventilated (Ashbaugh and Uzawa, 1968). The lungs, at autopsy, show diffuse hemorrhagic consolidation with blood stained pleural effusions. The airways are full of frothy blood stained secretions and, microscopically there is extensive alveolar and interstitial edema with areas of infarction. In the present study these changes were visible throughout all the histologic sections with prominent infiltration by polymorph nuclear leucocytes, suggesting pneumonic consolidation. No hyaline membranes were seen, probably because it was too early for their development (Orell, 1971).

Control Versus Hypothermia and Rewarming

Hemodynamic changes

The hemodynamic changes consisted of a fall in heart rate, systemic artery pressure and cardiac output over the initial two hour period after oleic acid injection in both groups. Cardiac output subsequently improved in the control group although heart rate remained low as did arterial blood pressure. These observations are similar to those of Ashbaugh and Uzawa (1968). Hillen et al (1971) found similar results in hemorrhage induced "shock lung" in monkeys. After two hours of shock, all their animals showed a 55-60% reduction in cardiac output which returned to near baseline levels after resuscitation. Powers et al (1972) found an increase in the cardiac output in the ARDS patients.

Hypothermic dogs had a sustained fall in cardiac output which is not entirely unexpected since blood pressure and cardiac output do fall with the induction of hypothermia. However, the degree of fall in cardiac output is of significance in the ARDS in as far as it decreases oxygen transport. There was a significant rise in pulmonary artery pressures (PAP) which is in agreement with the earlier observations with this model. Sealy et al (1966) found that pulmonary artery pressure increased to 149% of the control as compared to 150-250% reported by King et al (1971). The rise in PAP is much more marked than that observed in hemorrhage-induced shock lung models (Kounthwhaite et al,

1952; Keller et al, 1967). A rise in PAP despite a fall in cardiac output is meaningful since a rise under these circumstances indicates increased pulmonary vascular resistance which could be caused by extravascular fluid accumulation and/or hypoxic vasoconstriction. The increased pulmonary artery pressure may not be contributing to the pulmonary edema since, in the present study, pulmonary artery pressure never increased beyond 25 mmHg. Derks and Peters (1973) reported similar findings. An extrapolation from this would suggest that it is capillary leakage (Teplitz, 1968) that is, primarily, responsible for pulmonary edema. Hypothermia and rewarming did not affect pulmonary arterial pressure.

Lung Mechanics and Ventilation

There was a progressive fall at similar rates in lung compliance in both groups. Although hypothermia is believed to cause a decrease in pulmonary compliance (Severinghaus, 1959) this was not significant in this study. Sechzer et al (1958) found no change in lung compliance in anesthetised man when cooled to 29°C. Deal et al (1970) found a slight fall in compliance wth hypothermia in dogs but this was regained as the animal was rewarmed. However, if ventilation was maintained there was no change in compliance. Although no satisfactory explanations have been forthcoming regarding alterations in lung elasticity, the fall in surfactant production which occurs in association with hypothermia

(Bryan-Brown, 1973) may play some role since surfactant production depends on an adequate blood supply to the type II pneumocytes (Clements, 1970). It is perhaps only a conjecture that with the fall in cardiac output brought on by hypothermia, there is a decrease in pulmonary blood flow and hence interference with the production of surfactant. There was a similar tendency in the decrease of lung compliance in the two groups, perhaps due to the mild degree of hypothermia and the maintenance of positive pressure ventilation (Derks and Peters, 1973). As the experiment progressed, there was a greater fall in compliance, due presumably to airway obstruction, increasing alveolar and interstitial edema, microatelectasis and congestion as revealed on pathologic examination (Bergofsky, 1970).

A-aDO_2, Shunts and Dead Space Ventilation

The ARDS is characterised by increased venous admixture and absolute shunt reflected in a widened A-aDO_2. Wilson et al, (1969, 1970) found that the mortality increased with the degree of ventilation - perfusion mismatch, averaging 19% in patients with shunts less that 40%, 56% in those with shunts of 40-59% and 100% in seven patients who had shunts more than 60%. The term 'physiologic shunting' is actually a misnomer (Wilson et al, 1970) since what is being measured is "pathologic shunting" which is anywhere between 10-70% i.e., in excess of the normal or physiologic shunting. Shunting, in excess of this amount, is due to blood

primarily passing through the lungs from the pulmonary artery to the pulmonary vein without being oxygenated. This inability to oxygenate can occur if the blood either completely bypasses the pulmonary capillary system by going through anatomic shunts (Germon et al, 1968) or by passing through pulmonary capillaries perfusing nonventilated or collapsed alveoli. The ARDS leads to alveolo-capillary membrane instability with resultant interstitial and alveolar edema and hyaline membrane formation (Orell, 1971). In addition, there is a fall in functional residual capacity brought about by the increased lung stiffness (Powers et al, 1972; Monaco et al, 1972). All these factors lead to an increase in $A\text{-}aDO_2$. Other factors that may be operational are the role of cardiac output, pH changes and actual blockage of pulmonary capillaries by particulate matter (Teplitz, 1968; Blaisdell, 1974). If the cardiac output is high, theoretically the blood may flow through the pulmonary capillaries too rapidly to be completely oxygenated and hence $A\text{-}aDO_2$ may increase. Similarly blood entering pulmonary capillaries may be acidotic and will achieve a lower oxygen content at any given oxygen tension because of the right shift in the O_2 dissociation curve (Dowd and Jenkins, 1972).

There was an increase in $A\text{-}aDO_2$, venous admixture and absolute shunt in both groups with a greater increase in venous admixture in Group II as compared to Group I. This increase in venous admixture during hypothermia could be due

to an increased diffusion defect (Sproule et al, 1964) which becomes worse during hypothermia (Otis et al, 1957). However, its persistence during 100% oxygen breathing suggests that there was a gross increase in absolute shunt rather than any significant diffusion defect. An increase in $A\text{-}aDO_2$ observed in Group II dogs may also be explained on the basis of a decrease in $P\bar{v}O_2$ which was noticed in this group.

There was a relatively small increase in shunt in Group II dogs upon rewarming as compared to Group I. The exact mechanism for this difference is not clear. It may partly be explained on the basis of the lower cardiac output in Group II which caused blood to traverse through pulmonary capillaries at a slower rate and this allowed longer time for oxygenation. Ashbaugh and Uzawa (1968) observed that all animals in their studies died within five hours after the injection of 0.075 ml/kg body weight oleic acid. This suggested to them that the death was due to extreme blood deoxygenation as a result of increased ventilation-perfusion mismatch in the lungs. Obviously there is diffuse microatelectasis and arteriolar obstruction due to platelet and fat thrombosis with resultant ventilation of non-perfused units. Markedly impaired perfusion leads to an increase in the dead space ventilation which is in fact wasted ventilation leading terminally to hypercarbia. This imbalance actually produces a situation where one portion of the lung is being ventilated but not perfused and the other

portion being perfused but not ventilated (Moore, 1968; Dowd and Jenkins, 1972). Hypothermia did not have any significant effects on the absolute shunt and dead space ventilation, but the dead space ventilation did increase upon rewarming due to a fall in the cardiac output observed in this group.

Hypothermia has been shown to cause an increase in physiological as well as anatomical dead space ventilation due to bronchodilatation (Severinghaus, 1959) although this effect does not seem to be operative in the hypothermic ARDS model. However, the increase in dead space ventilation upon rewarming may be a reflection of the balance between effective circulating fluid volume and pulmonary circulation. During surface cooling there is peripheral vasoconstriction and a shutdown of peripheral vascular bed to maintain the central flow. With rewarming peripheral perfusion increases, there is a relatively greater fall in effective circulating fluid volume and the acidotic blood circulating through the pulmonary capillaries leads to further pulmonary arteriolar constriction with low pulmonary perfusion and hence, an increase in dead space ventilation (Kim and Shoemaker, 1973).

Oxygenation of Blood

Mohri et al (1974) showed that there was no change in the arterial PO_2, arterial oxygen saturation and oxygen content of the arterial blood in normal dogs subjected to hypothermia. However Dill and Forbes (1941) observed a

slight fall in arterial PO_2 during hypothermia. Similarly venous PO_2 did not show any change until the temperature decreased to below 25°C. Group II dogs showed a significant fall in arterial PO_2 during hypothermia as well as on rewarming when the decrease was significant as compared to Group I. The fall in arterial PO_2 during hypothermia corresponded to the increase in absolute shunt and dead space ventilation which led to progressive deoxygenation and hypoxemia. This situation may have been accentuated to some degree by a diffusion defect (Dill and Forbes, 1941; Otis et al, 1957). There may also have been a minor contribution to decreased oxygenation due to the slowing of chemical reactions during hypothermia which are concerned with oxygen extraction in the lungs (Dill and Forbes, 1941). $P\bar{v}O_2$ also fell during hypothermia with further fall observed on rewarming in Group II as compared to Group I which was maintained at normothermia throughout the experiment. The fall in $P\bar{v}O_2$ is perhaps secondary to the decreased cardiac output, low PaO_2 and shift of the Oxygen dissociation curve to left. Mixed venous oxygen tension closely portrays the adequacy of tissue oxygenation as it represents something close to the mean capillary oxygen tension of blood returning from tissues (Finch and Lenfant, 1972). It is a function of cardiac output, metabolic rate and oxygen consumption. A decrease in $P\bar{v}O_2$ indicates either a reduction in oxygen supply to the tissues or an increase in tissue oxygen utilization. Group I dogs maintained a nearly

constant $P\bar{v}O_2$ throughout the experiment since oxygen delivery kept pace with the oxygen demands. This was not the case in Group II where the balance between oxygen delivery and consumption was disturbed during hypothermia as well as during the process of rewarming and after the animals were restored to normothermia.

Oxygen supply can also be evaluated by consideration of other factors such as arterio-venous oxygen difference ($a-vO_2$ difference). This again indicates the extent to which cardiac output matches the tissue metabolism and tissue oxygen demands. A normal arterio-venous oxygen difference with normal tissue metabolism indicates a normal oxygen delivery regardless of hemoglobin concentration, oxygen saturation and affinity of hemoglobin for oxygen (Finch and Lenfant, 1972). Mohri et al, (1974) found no change in arterial oxygen contents although arterio-venous oxygen difference decreased with hypothermia. Fisher and his colleagues (1957) showed that as long as the cardiac output was stable for ten to twelve hours of hypothermia, the arterio-venous difference remained unchanged. However, with prolongation of hypothermia to eighteen hours or more, the difference in arterial and venous oxygen contents increased suggesting onset of stagnant hypoxia due to a low cardiac output. In the present study, all the factors mentioned above were altered in one way or another in each group. The arterio-venous oxygen content remained nearly unchanged in the normothermic dogs (Group I) since the tissue metabolic

rate and cardiac output changed very little, if at all, after the initial two hour post-oleic acid injection period. Hypothermia reduced the tissue metabolic-rate but also decreased the oxygen supply to the tissues even at the moderate temperature of 34°C. Presumably metabolic rate did fall as evidenced by the fall in oxygen utilization but the transport of oxygen fell even more so that the tissues had to extract large amounts of oxygen from the circulating blood thus leading to an increase in the arterio-venous oxygen difference. This is also reflected in the finding of diminished arterial oxygen content in the second group of dogs. Although oxyhemoglobin dissociation curve and P50 were not measured, it is understandable that the left shift of the hemoglobin dissociation curve with hypothermia may also have had a role to play in decreasing the venous PO_2. However, others feel that there is no demonstrable shift in the dissociation curve with hypothermia because a metabolic acidosis often develops during hypothermia (Ballinger et al, 1961). It was shown by McConn et al, 1971) that acute severe illness per se is associated with an initial leftward shift of the dissociation curve. This factor could possibly have contributed to left shift of the hemoglobin dissociation curve secondary to a fall in body temperature. At the same time Longmuir (1962) reported an increased affinity of tissues for oxygen as the body temperature was decreased and concluded that when blood and tissues are cooled together there is no imbalance in the respective affinities for

oxygen in the tissues and hemoglobin except, perhaps at lower temperatures in the range of 20-30°C. It would be safe to conclude from the above discussion, however, that there must have been a leftward shift of the oxygen dissociation curve in the hypothermic dogs since these dogs were definitely more hypoxemic as compared to the normothermic dogs in Group I. The leftward shift of the oxygen dissociation curve would also account for the significant fall in venous oxygen tension observed in Group II. Another factor that can contribute to increased arterio-venous oxygen content difference would be an increased hemoglobin concentration in the blood. This is unlikely to have had any significant effect on differences between the two groups since the concentration of hemoglobin rose in both groups to a similar degree during the entire experiment.

Oxygen Consumption versus Oxygen Delivery

The relationship between oxygen supply and demand in the two groups is shown in Figure 15. A net result of hypothermia and rewarming was reduced oxygenation by the lungs due to an increase in the calculated shunt and dead space ventilation. There was a fall in oxygen transport secondary to a fall in both cardiac output and arterial oxygen content. Oxygen consumption did fall but the decrease in oxygen consumption was disproportionate relative to the fall in oxygen delivery resulting in oxygen debt and tissue hypoxia exaggerated from the pre-hypothermic level.

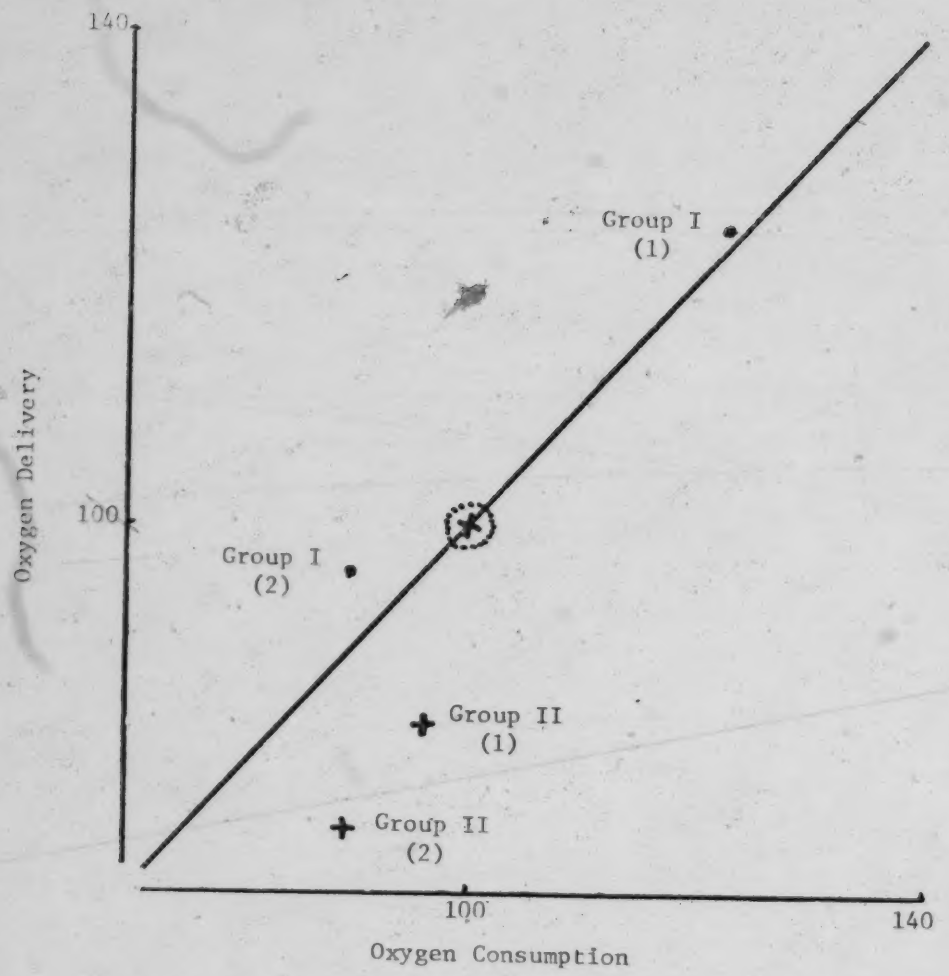

Figure 15 Oxygen transport vs oxygen consumption in Group I (•) and Group II (x) expressed as percentages of the post-oleic acid values (⊗). 'I' and '2' represent the first and second periods.

Interference with oxygen delivery appears to be due primarily to a fall in cardiac output and arterial oxygen content. It has been reported that the stroke volume of heart is as large at 18°C as it is at 38°C (Adolph, 1956). Bigelow and his colleagues (1950) and Rosenhain and Penrod (1951) found that the overall delivery of oxygen to the tissues does not decrease during hypothermia; in fact, these authors found that the arterio-venous oxygen content difference was about the same at 18°C as it was at 38°C. Kao (1955) felt that although cardiac output decreased with hypothermia in normal dogs, it was still more than adequate to transport sufficient oxygen at the low levels of oxygen consumption induced by hypothermia. Similarly, it has been observed that although heart rate falls with induction of hypothermia, it has a salutary effect on the cardiac filling and in fact, improves stroke volume even in critically ill febrile patients who invariably have tachycardia (Williams and Cavanagh, 1970).

What then explains the observed marked fall in oxygen delivery and cardiac output observed in Group II? To answer this question two more factors need to be taken into consideration. These are: a) fluid balance and b) the ventilatory functional status. There was an increase in the concentration of hemoglobin and hematocrit (10 to 17%) in both groups soon after the injection of oleic acid. This finding may have been secondary to some loss of intravascular fluid into the lung interstitium as evidenced

by the appearance of hemorrhagic and frothy seretions in the tracheo-bronchial tree which was observed to a similar degree in all the dogs. Hence one would expect a similar fall in heart rate and arterial pressures in all the dogs. This was shown to be so (Table III and Figure 4). Both groups had a similar and persistent fall in heart rate and blood pressure throughout the experiment. D'Amato and Hegneur (1953) observed a 12% fall in plasma volume when the body temperature was lowered to 20°C. From this observation, it can be assumed that there would be a relatively insignificant fall in the plasma volume at 34°C. Hence it is unlikely that the fall in cardiac output can be explained entirely on the basis of sequestration of body fluids and blood other than that induced by oleic acid. Halmagyi et al, (1973) found that a combination of mild hypothermia (30 to 32°C) and volume expansion effectively improved tolerance to both hemorrhage and endotoxin and that oxygen transport was maintained at the same level as in control dogs. However, they observed that "large amounts of fluids" were required to maintain oxygen transport. This is understandable in their study since these authors were dealing with a syndrome of reduced effective circulating fluid volume as a result of the very nature of their experiment i.e., acute bleeding and the injection of endotoxins. Endotoxin is known to lead to marked dehydration due to sequestration of fluids in venous and capillary capacitance bed in the body. It has been shown earlier that only minimal hemodynamic changes occur in the

oleic acid induced experimental model. Although it is true that dogs in the present study did lose some blood and fluids in the form of increased endotracheal secretions and pleural effusion, this factor is unlikely to have been a major cause for the different trend seen in decreased cardiac output in the two groups. No attempt was made to volume load these dogs, as suggested by Halmagyi and his co-workers (1973) since the "large amounts of fluids" as required in their dogs might have further jeopardised lung function in the present study by leading to an increase in the alveolar and interstitial edema (Mills, 1968; Zimmerman et al, 1971).

Decreased PaO_2, arterial oxygen saturation and arterial oxygen content point to defective oxygenation in the lungs. This is in sharp contrast to the observations of Dill and Forbes (1941) and Rosenhain and Penrod (1951) who found that even at temperatures as low as 18 to 24°C ventilation, albeit decreased, was more than adequate to deliver oxygen to the lung alveoli with subsequent exchange with blood as indicated by the presence of high concentrations of arterial oxygen and low carbon dioxide tensions. Adolph (1956) felt that hypothermia, far from producing hypoxia, in fact, increased tolerance to it and prolonged the endurance for hypoxia. Apparently there were some changes in the lung structure itself that may have been responsible for defective oxygenation of blood which were not operating in Group I. Hyopthermia used for prolonged periods has been

known to lead to micro-atelectasis and congestion (Fisher et al, 1957). Swan (1956) demonstrated frank edema in his experiments. Earlier Dill and Forbes (1941) noted development of pulmonary edema in one patient from which it was concluded that there may be an accumulation of fluid in the alveoli at reduced body temperatures. From the above discussion it appears that there was a deterioration of pulmonary functions in hypothermic dogs which resulted in marked hypoxemia of greater magnitude than observed in the normothermic dogs. The arterial hypoxemia was complicated to some extent by the fall in cardiac output as a result of increased acidosis (respiratory as well as metabolic) demonstrated on rewarming. Hypoxemia may also have led to the myocardial depression due to reduced availability of oxygen. The net result of these changes was a severe diminution of the transport of oxygen to the tissues leading to the earlier death of dogs subjected to hypothermia.

CHAPTER 5

Summary and Conclusions

Summary

In summary, it appears from this study that hypothermia led to worsening hypoxemia and oxygen delivery by a number of mechanisms, principally a deterioration of the ventilaton-perfusion mismatch which was perhaps due to an increase in the pulmonary congestion induced by hypothermia. Other contributory factors may have been the fall in fluid volume and a decrease in cardiac output. The net result was an oxygen delivery less capable of meeting the tissues' oxygen demands in the hypothermic group compared to the control (normothermic) group. Dogs cooled to 34°C after inducing the ARDS became more hypoxic than the control dogs maintained at 37°C. Probably, hypothermia itself was responsible for the deterioration in the oxygenation of blood as well as its transport to the tissues. The deterioration in oxygenation may account for marked hypoxemia and acidosis seen in the dogs that died between 14-18 hours in Group II. In contrast, most of the dogs in Group I survived beyond 22 hours.

Conclusions

Blair (1964) remarked that "Hypothermia has never cured anything, does not now and never will". This is because hypothermia, in the strictest sense, is not a therapeutic agent. Hypothermia is, at best, an adjunct and that is how it has been known and handed down from the physicians of ancient times to the present day scientists.

In spite of the use of hypothermia for a number of years and recently a resurgence of interest in its use, nothing really is known as to the mechanism by which hypothermia may be acting as an adjunct save the observation that it reduces tissue breakdown and conserves "crippled homeostasis" (Blair, 1964). Swan (1973) considered it strange that so many doctors over the years had recommended the use of a modality which was clearly patho-physiological. Hypothermia has been credited with causing a decrease in tissue oxygen demands. The fall in oxygen consumption has been frequently documented with studies in healthy animals, although nothing is known about its role in patients with acute respiratory insufficiency. The present study, carried out in severely hypoxemic dogs, demonstrated that the fall in oxygen consumption was far less significant than the corresponding fall in oxygen delivery to the tissues resulting in exaggerated hypoxemia.

There is still a great deal of interest in the use of hypothermia and it may well be that with better control of acid-base status, cardiac activity and fluid balance, the

technique may be useful. In the present study, it is possible that if control of acidosis had been introduced into the protocol, there may have been more respectable survival figures following the use of hypothermia. Perhaps, there may also have been less marked pulmonary edema as a result of properly controlled acidosis. It is equally conceivable that in critically ill patients with circulatory failure a reduction in body temperature may depress the circulation even more profoundly and the resulting paradoxical effect could accentuate the unfavorable balance between oxygen supply and demand so that it might be advantageous to restore fluid balance in an effort to increase oxygen transport. However the administration of fluids needs to be taken in the light of documented evidence that fluid overload has detrimental effects on pulmonary function in the ARDS patients.

This was a small study but it has helped to shed light on the adverse effects of hypothermia on oxygen transport. It is clear that additional experimental and/or clinical studies are needed wherein the factors of fluid and electrolyte balance, correction of acidosis and maintenance of adequate oxygenation by ventilatory adjustments are investigated with and without hypothermia in hypoxemic failure. Such a study may resolve the conflicting reports in the literature, if correcting the above parameters would actually improve tissue oxygen supply with the institution of hypothermia.

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